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second part of this book is devoted to *Nutrition in Disease*. the author describes the physiologic and pathologic changes of body due to disease, then gives complete directions on what diet to prescribe to meet the problem at hand. Clinical word-pictures are painted, stressing pathologic changes, the physiologic disturbance, and pointing out how the intake of certain foods will tend to correct—or help correct—the condition. Menus for each day of the week are given, with food quantities given in household or kitchen terms as well as in metric and standard measures. The final section of the book gives special methods of feeding, detailed tables of food values, cooking suggestions, and the chemical composition of American food materials.

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CLINIC OF DR. JOSEPH LEE HOLLANDER

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THE DIAGNOSIS AND TREATMENT OF GOUT

GOUT is a chronic disease of purine metabolism, and is characterized by sudden seizures of pain in one or more joints, with swelling, discoloration, and tenderness of the part. Prolonged disturbance of purine metabolism leads to characteristic depositions of sodium biurate in the periarticular and perichondrial tissues. These deposits, or tophi, when identified are diagnostic, but it is important that the disease be recognized when these lesions are absent. They do not occur in approximately 60 per cent of cases of gout.

Gout without tophi has been designated by Hench (1936) as *presumptive* or *pretophaceous* gout, in contrast to the late *tophaceous* form. Vague terms such as "abarticular gout," "irregular gout," "retrocedent gout," and "gouty diathesis" have been devised to include possible manifestations of the disease in other than periarticular tissues.

It must be realized that gout is not a local disease. It manifests itself locally, but it is well to consider the whole body as being gouty.

CASE REPORTS

Case I.—A. S., a white male aged sixty-nine. He was a retired dentist. There was no history of gout, fibrositis, or arthritis in his family. The patient's personal habits were regular, though he was a heavy eater since boyhood and was very fond of meat and rich food, and he only rarely used alcoholic beverages. His past history was negative except that, for twenty-five years he had

suffered from repeated attacks of pain in the left lumbar area. This pain was referred to the groin. Dysuria and frequency of urination accompanied the attacks, but there was no hematuria. On several occasions he was thoroughly examined by urologists who took pyelograms and roentgenograms of the spine but found no cause for his pain. In the last few years the attacks had been less frequent, occurring only once or twice a year.

The first attack of joint pain occurred in February, 1938. The patient was then on a vacation in Florida, where he admittedly over-ate. At two o'clock one morning he was awakened by a boring, burning pain in his left great toe. The toe became swollen and purplish in color and was excruciatingly tender. By morning the pain had subsided but the foot remained too tender to allow a shoe to be worn. On three successive nights the pain recurred with undiminished intensity.

The patient was first examined on the third day of the attack. At this time the physical examination showed him to be overweight and in acute pain. His temperature was 99.4° F. and the pulse rate 96 per minute. The heart was slightly enlarged, and there were many premature contractions. The blood pressure was 158/100 and there was a generalized arteriosclerosis. The left great toe was swollen, purplish, the skin was quite glossy, and it was tender even on slight pressure.

The urine contained a trace of albumin and a few casts. The blood count was normal except for 10,700 leukocytes per cu.mm. The blood uric acid level was 7.2 mg. per 100 cc. The Wassermann and Kahn reactions were negative. Roentgenographic examination of the left foot revealed several distinct punched-out areas in the distal end of the first metatarsal, with some osteoarthritic change of the joint.

Colchicine, $\frac{1}{20}$ grain (0.5 mg.), was given every three hours for nine doses when the onset of diarrhea necessitated a change of therapy. A liquid, purine-free diet was prescribed. Within twenty-four hours the pain had almost disappeared and the swelling of the joint was subsiding.

After the acute attack was under control, prophylactic treatment was begun. A diet low in purines was prescribed. The patient was advised to drink water freely and to take neocinchophen, $7\frac{1}{2}$ grains (0.5 Gm.), three times daily for the first three days of each fortnight.

For seven months the patient adhered to the prescribed regimen and was free of pain. The pain in the back previously complained of did not recur. In September, 1938, while on a holiday, the patient became wet and chilled. Next day he was seized with severe pain in the right shoulder radiating down the arm. When seen on this occasion he had a temperature of 99.6° F., slight nasal congestion, and the skin over the flexor surface of the forearm was hyperesthetic. Peripheral neuritis was believed to be the cause for the pain. One day later, however, the right shoulder joint became painful and tender and slightly swollen. The temperature rose to 102° F. and the pain became so intense that morphine was administered. The local application of heat afforded some relief. Colchicine, $\frac{1}{20}$ grain (0.5 mg.), every four hours, was started on the following morning. The pain in the right shoulder decreased during the day, but late that evening the left shoulder suddenly became excruciatingly painful, with pain over the left side of the chest and down the left arm. This was so severe and the patient was so prostrated that a cardiac infarct was suspected, but electrocardiographic tracings were normal. The symptoms subsided in three days. During this time he received colchicine, $\frac{1}{20}$ grain, every four hours, and the diet was restricted to fluids low in purine content.

Interval treatment of a low-purine diet and neocinchophen was resumed

and the patient remained well for six months. Again on his annual trip to Florida, while staying overnight in Savannah, he was seized with severe pain in the left shoulder, with radiation down the arm. The attending physician made a diagnosis of coronary artery occlusion and prescribed absolute rest in bed and administered morphine. The patient suspected that the attack might be an exacerbation of gout and began taking colchicine, with complete remission of the symptoms in two days. He had been careful to follow his diet except for indiscretions while away from home, and he was finally convinced that he must limit himself to the prescribed foods. In the months since this last attack the patient has been symptom-free. The blood uric acid level, four weeks after the last attack, was 4.8 mg. per cent. A roentgenogram of the left shoulder has shown no gouty change. No tophi have been observed.

Case II.—V. W. was a white female aged sixty-eight years. Her father and uncle had both had severe attacks of "rheumatism" during their later years of life.

The patient's diet was abundant, and contained large amounts of meat, but she denied the use of any alcoholic beverage. She was quite poor, and had done heavy housework all her life. Joint pains were first noted in 1936, when both "bunion joints" became swollen, red, and tender. This pain was moderate, continuous, but worse at night. The pain persisted for several weeks, during which time the right knee and the left wrist became involved as the feet improved. Mild recurrences of the pain were observed every few months since the onset, often in previously unaffected joints.

In 1937, the patient noticed a tender lump about the size of a split pea on the margin of the right ear. A few months after this a small tender lump appeared at the base of the left great toe. This became so painful that she was forced to wear house-slippers instead of shoes. A small ulcer appeared a short time later over the base of the right great toe. From this ulcer a little chalky fluid exuded from time to time. Later, a similar ulcer developed over the painful joint of the left great toe. The patient applied various proprietary ointments to the affected areas, but without avail.

Early in 1938, the middle joint of the third finger of the left hand became swollen and tender, and after several months an ulcer developed over this joint. The lump on the margin of the ear broke down, discharged for several weeks, and then healed spontaneously. The patient first sought medical advice, not for these conditions, but for a "head cold."

On physical examination the patient appeared to be well nourished but was not obese. Signs of a typical, upper respiratory tract infection were observed. The heart was enlarged to the left. There were a few premature contractions, and a blowing systolic murmur was audible at the apex. The blood pressure was 162/104, and arteriosclerosis was quite marked. No signs of cardiac decompensation were noted. A small indurated scar was found on the outer margin of the right ear. Several finger joints were enlarged, and over the left third finger there was a small, punched-out ulcer. On the mesial aspect of the base of both great toes was an ulcer, approximately 5 mm. in diameter, with induration around the area. A milky fluid was expressed from the ulcer on the left foot. This contained many needle-shaped crystals when seen under the microscope. This examination was carried out on exudate from the other ulcers, and similar crystals were found. The patient refused to enter the hospital and, because of the economic conditions, the studies were limited. The urine on several occasions contained a trace of albumin, a few pus cells, and a few granular casts. The blood count was normal. The blood Wasser-

mann and Kahn reactions were negative. The fasting level of the blood sugar was 95 mg., the blood urea nitrogen 9.5 mg., and the blood uric acid 3.9 mg., per 100 cc.

Treatment consisted of a low-purine diet, three-day courses of neodincho-phen every two weeks, and local treatment of the ulcers. These lesions were thoroughly excised under local anesthesia and were healed completely within two weeks. The subsequent course has been uneventful.

Case III.—N. DeM., an Italian aged fifty-two years, had been a stone-cutter for thirty years. His family history was negative for rheumatism, gout, or fibrositis. The patient admitted dietary excesses; he had a particular preference for meat and seafood, and often made a meal of nothing but bread and meat. He drank four or five glasses of beer daily for many years. The present illness began in 1935 with an acute attack of pain and swelling in the dorsum of the left foot. In a day or two this pain began to subside, but the right ankle became swollen and painful. As this joint improved, the right knee, left shoulder, and right elbow became involved in turn. The patient was forced to remain in bed for three weeks but sought no medical advice. Similar attacks of joint pain recurred from two to five times a year, but the patient noted no seasonal incidence. The attacks often, though not always, began at night, sometimes involving only one joint but usually several. The patient finally came to the Pennsylvania Hospital because of a slowly progressive cough and a recurrence of the joint pain.

The physical examination on admission revealed a short, stocky man with moderate orthopnea. His chest was markedly emphysematous, expansion was limited, and harsh breath sounds and musical râles were audible throughout both lungs. The middle joint of the third finger of the right hand was swollen, hot and tender, and there was swelling, redness and tenderness over the dorsum of the right foot. No tophi were found. The body temperature on admission was 99.6° F., and the pulse rate was 100 per minute.

Examination of the urine on several occasions showed no abnormality. The blood count was normal except for 10,600 leukocytes per cu.mm., with 76 per cent neutrophils. The blood uric acid level on admission was 6.2 mg. per 100 cc., and the Wassermann and Kahn reactions were negative. The gonococcus complement-fixation test was negative. The erythrocyte sedimentation rate was 16 mm. in one hour, and the hematocrit reading was 45 (Wintrobe). Roentgenographic studies of the chest showed a moderately advanced silicosis. Roentgenograms of the feet showed advanced osteophyte formation about both first metatarsal joints but no areas of bone rarefaction.

Following a three-day period of treatment consisting of rest in bed and the administration of salicylates, the body temperature and pulse rate returned to normal. The swelling of the joints subsided and the pain gradually disappeared. An attempt was made to provoke another acute attack by allowing the patient a high purine diet. On this regimen the blood uric acid increased to a fasting level of 9 mg. per 100 cc. and the excretion of uric acid rose from 0.25 Gm. to 0.55 Gm. per day, but no attack of gout was produced. The patient was discharged from the hospital free of symptoms. During his stay he received instructions in the preparation of a diet low in purines.

Since this patient's discharge he has been seen periodically in the Arthritis Clinic. He has had one attack of joint pain in nine months since his stay in the hospital. He admitted that after disregarding his diet for several weeks he was suddenly seized during the night with severe pain in the left foot. The next morning he limped into the clinic. Examination showed swelling,

tenderness, and some discoloration over the dorsum of the foot. He was given colchicine, $\frac{1}{120}$ grain (0.5 mg.), every four hours for ten doses. There was a complete remission of symptoms in thirty-six hours. Following this attack, neodinophen, $7\frac{1}{2}$ grains (0.5 Gm.), has been given three times daily on the first three days of each fortnight. A determination of the blood uric acid level on two occasions has revealed a concentration of 6.8 mg. per 100 cc. There has been no recurrence of pain in the joints.

COMMENT

The three cases reported were chosen as illustrating different forms of gout and the problems encountered in the diagnosis and in the treatment.

In the first case the diagnosis was a simple matter because the clinical picture was typical. The previously existing pain in the back may have been due to gout. Many authors claim that gout exists for from eight to fifteen years before it becomes obvious. The later attacks of pain in the shoulder serve to show how the condition may be readily confused with other diseases. In the classification of Hench (1936), this case is Stage I—acute recurrent gouty arthritis with complete remissions. No tophi were seen, but bone changes were visible roentgenographically. The response to colchicine was definite in each attack. The level of the blood uric acid was elevated during the acute attack, but was within normal limits in the interval between attacks.

The second patient, the woman with tophaceous gout, was quite unusual. Hench and others have found that only 3 per cent of patients with gout are women. Thomsen states that gout in women is usually of the irregular type, appearing clinically like rheumatoid arthritis and only occasionally in the classic form. In this patient the acute phase might well have been regarded as rheumatoid arthritis. The development of tophi, and their subsequent superficial ulceration, made manifest the true nature of the disease. The distribution of the tophi was typical and their crystalline content easily demonstrable. It is generally agreed that the demonstration of tophi establishes a diagnosis of gout. The uric acid level was not elevated, and roentgen-ray studies were not done. This patient, as well as the first one, had generalized arteriosclerosis and heart disease. Apparently this case would be classed by Hench as Stage II—chronic gouty arthritis with tophi.

The third patient presented an atypical picture of gout. The history is not particularly different from that of rheumatoid arthritis, except that more joint deformity might be expected in event of the latter in a four-year period. There were no punched-out areas in the bone shadows in the roentgenogram, but there were advanced osteophyte formations. Some authors regard the formation of osteophytes as a late change after calcification or resorption of a urate deposit. The fact that the ends of the first metatarsals are the most frequent sites for the formation of tophi, and that these were the locations of the osteophytes, might be significant here. In this case the elevated blood uric acid levels in the absence of nephritis confirmed the diagnosis. Furthermore, the response to colchicine was definite. Arteriosclerosis was not evident in this patient. The classification of this case, according to the plan of Hench, would be Stage I, Phase 2—or acute recurrent arthritis with hyperuricemia and complete remissions between attacks; tophi absent.

The outstanding features of these three cases of gout are summarized in Table 1.

DIAGNOSIS OF GOUT

Hench (1938), in discussing the criteria for the diagnosis of gout, noted twenty points expressed axiomatically. These points give such a complete summary of the subject that they are quoted here:

"Suspect gout when acute arthritis suddenly develops:

1. After relatively trivial trauma
2. After dietary excesses of holidays, birthdays, and lodge nights
3. After any surgical operation (acute postoperative arthritis is usually gouty)
4. After the trauma, exposure, and dietary insults of a hunting or fishing trip
5. In the spring or fall (gout has a definite seasonal incidence)
6. In the night between 2 and 7 A. M. (it may occur at any hour, however)
7. In patients under certain coincidental treatments, such as

TABLE 1
THE SALIENT FEATURES OF THREE CASES OF GOUT

	Case I.	Case II.	Case III.
<i>Etiology</i>	Overeating. Obesity.	Overeating. Hereditary factor.	Overeating. Beer. Obesity.
<i>Symptoms:</i> Onset	Sudden seizure of toe pain at night, typical "podagra."	Acute arthritis in both feet—not typical seizure.	Acute arthritis in foot and other joints. Not typical seizure.
Later attacks	Shoulder pain—sudden seizures after holiday.	Inflammation in many joints, never severe or sudden seizures.	One sudden seizure of pain in foot at night.
<i>Objective findings:</i> Physical examination	Great toe swollen, very tender, purple. Later attacks—left shoulder tender and swollen. Patient overweight.	Ulcerating tophi on right ear, both great toes and left third finger.	Swelling, redness, ten- derness of ankle and finger joints. Patient overweight.
Blood chemistry . . .	Uric acid: 7.2 mg. % in attack. 4.8 mg. % in interval.	Uric acid 3.9 mg. % Urea N 9.5 mg. % Sugar 95 mg. %	Uric acid: 6.2 mg. % in attack. 6.8 mg. % in interval.
Blood count	Leukocytosis (10,700).	Normal.	Leukocytosis (10,600).
Urine	Albumin, casts.	Albumin, casts.	Normal.
Röntgenograms . .	Punched-out areas of negative density in first metatarsal of left foot.	None taken.	No punched-out areas in bones. Osteophyte formation on both first metatarsals.
Examination of tophi	None.	Exudate full of sodium bismate crystals.	None.
<i>Course</i>	Recurrent acute attacks with complete remis- sions.	Chronic after first at- tacks	Recurrent acute attacks with complete remis- sions.
<i>Treatment:</i> In attacks	Purine-free diet. Colchicine. Symptomatic measures.	None.	Purine-free diet. Colchicine.
In remissions . . .	Low-purine diet. Neocinchophen.	Low-purine diet. Neocinchophen.	Low-purine diet. Neocinchophen.
<i>Complications</i> . . .	Arteriosclerosis with heart disease.	Arteriosclerosis with heart disease.	Silicosis.

liver diet for pernicious anemia, ketogenic diet for bacil-
luria, salyrgan for dropsy, ergotamine tartrate (gyner-
gen) for migraine, or insulin for diabetes

8. In patients with polycythemia or leukemia
9. In females, only with extra caution as this is rare
10. In men over forty years of age (this is the most common
form of acute arthritis in this group).

"Suspect gout:

11. When acute arthritis comes on with dramatic speed, in a
few minutes or hours

12. When the pain is unusually severe, 'the worst ever'
13. When the great toe is acutely, not chronically, involved (podagra, however, may occur late or never in the course of the disease)
14. When maximal tenderness is at the mesial aspect rather than underneath or on top of the 'bunion joint'
15. When the appearance of an involved foot is suggestive (warm, bluish-red rather than cold, bluish-white as in atrophic arthritis), with edema and later desquamation of skin
16. When an acute arthritis of short duration (one to three weeks) and full restitution of function occurs
17. When acute recurrent attacks of arthritis occur with complete remissions, possibly followed by chronic arthritis later
18. When olecranon bursitis is discovered or a positive history obtained (this is several times more common in gout than in any other disease)
19. In patients with acute or chronic arthritis who have or have had chronic nephritis or renal colic (urate stones or gravel incidentally cast no roentgenographic shadow)
20. In a case presenting a number of the above features even when podagra (a common, but not inevitable, feature), hyperuricemia, 'characteristic' roentgenographic changes, and tophi are absent. These are not early, but rather later features of gout."

Many otherwise undiagnosed cases of gout may be brought to light by observing the above suggestions. The successful use of colchicine as a therapeutic test (this drug often terminates an attack with dramatic rapidity) may serve to support the diagnosis of gout. Repeated determinations of the blood uric acid level may be necessary to discover a transient elevation. Jacobson found that the blood uric acid values in gouty patients ranged from 5.2 mg. to 14.8 mg. per 100 cc., whereas the values in normal individuals for the blood uric acid seldom exceeded 6 mg., and the average was 4.2 mg., per 100 cc.

Roentgenograms of the affected joint in a suspected case of gout often will confirm the diagnosis if punched-out areas of negative density are noted in the bone adjacent to the joint. A

biopsy of tophi in the subcutaneous tissues can easily be made and the contents studied microscopically. The needle-like crystals of sodium biurate may be seen in the exudate, or a positive murexide test applied to the material shows the presence of urates.

Gout may be confused with traumatic, infectious, or osteoarthritis, or with rheumatic fever, but when gout is suspected and the patient studied accordingly, the diagnosis is seldom missed.

TREATMENT OF GOUT

General Measures and Prevention.—The patient who is predisposed to gout or who is known to have gout will do much to prevent attacks by practicing moderation. Excesses of foods rich in purines are to be avoided. Abstinence from alcohol, adequate rest, avoidance of fatigue and exposure to extremes of temperature will aid in keeping the disease under control. Obesity is corrected by reducing the caloric intake, and moderate exercise is helpful.

Prophylactic Treatment.—Impending acute attacks of gout may be recognized by excessive appetite, indigestion, irritability, depression, twinges of pain in the joints, and diuresis. Prompt treatment will serve to alleviate or prevent the attack. In addition to the general measures already outlined, the patient should observe a diet excluding purine-rich foods (see Table 2), should drink large amounts of water, and keep elimination free by taking a saline laxative. Neocinchophen (tolysin) 0.5 Gm. ($7\frac{1}{2}$ grains) three times daily for two or three days each fortnight is a valuable prophylactic measure. This drug is contraindicated when an idiosyncrasy to it is suspected or when biliary tract disease is present.

Management of the Acute Attack.—The patient is confined to bed, and the affected joint is elevated and kept warm. Hot moist dressings of magnesium sulfate are soothing. Fluids are given freely. The diet is practically purine free and bland. The following menu is suggested: *Breakfast*—fruit juice, cereal with cream and sugar, toast (white bread) with butter, and coffee (contains methylated purines, apparently not harmful) with cream and sugar. *Lunch*—cream soup (tomato or vegetable), bread, butter, milk, and fruit. *Supper*—eggs (any

style except fried), baked or mashed potato, buttered carrots or beets, bread, butter, milk. Dessert: vanilla ice cream, custard, or gelatin.

If the pain is intense, morphine sulfate 0.01 Gm. (gr. $\frac{1}{60}$) may be given subcutaneously for relief. Colchicine, the alkaloid of colchicum, in oral doses of 0.5 mg. ($\frac{1}{120}$ grain) every three or four hours is specific for the acute attack of gout. This drug does not increase the excretion of uric acid, but apparently acts as an anodyne. Colchicine is most effective when increased to the point of looseness of the bowels. Vomiting, purgation, and tenesmus are symptoms of overdosage, in event of which the drug should be stopped and a smaller amount resumed after the intoxication has subsided. Nothing is to be gained by continuing colchicine after the pain is relieved. As soon as the acute attack has subsided, the measures outlined for treatment of chronic gout should be started in order that a recurrence may be prevented.

Treatment of Subacute, Chronic, or Atypical Gout.—A low purine diet is of distinct value for these forms, with drugs second in importance. Abstinence from the use of alcohol is important. The diet has a low purine content, and the total caloric allowance should be adjusted to reduce the body weight and maintain it at a slightly substandard level. It is as important to control the quantity of food as well as the type of foods allowed. The diet list in Table 2 has proved helpful in managing these patients.

In patients whose gout is moderately active, the choice of foods should be confined to those in column 3, with one selection daily from those in column 2, and one selection from column 1b not oftener than every ten days or two weeks. The choices may be more liberal when the gout is inactive.

An illustrative menu for a low purine diet is as follows:

Breakfast: fruit, cereal (e.g., Cream of Wheat) with milk and sugar, soft boiled egg (two if desired), toast, butter, coffee with cream and sugar.

Lunch: omelet or cottage cheese, fruit or vegetable salad, bread, butter, tea or coffee with cream and sugar. Dessert: ice cream or pudding or custard or gelatin.

Dinner: small serving of meat or fish (column 2 of Table 2), potato or rice or spaghetti, buttered or creamed vegetable

TABLE 2

THE GROUPING OF FOODS ACCORDING TO THEIR PURINE CONTENT

1	2	3
Foods that contain a large amount of purine	Foods that contain a moderate amount of purine	Foods that contain no purine
	(a)	
Sweetbreads	Chicken	Milk
Liver	Mutton	Eggs
Kidney	Bacon	Cheese
Squab	Oysters	Caviar
Calf's tongue	Herring	Shad roe
		Nuts
	(b)	
Turkey	Salmon	Gelatin
Pork	Lobster	Sugar and sweets
Veal	Crab	Coffee*
Sausage	Whitefish	Tea*
Beef	Asparagus	Cocoa*
Goose	Lima beans	Fats of all kinds
Anchovies	Navy beans	Fruits of all kinds
Sardines	Kidney beans	Cereals (except whole grain)
Trout	Kohlrabi	Bread (except whole grain)
Pike	Onions	Vegetable soup (made without meat)
Perch	Peas	Vegetables of all kinds except those listed in columns 1 and 2
Codfish	Spinach	
Lentils	Mushrooms	
Gravies	Oatmeal	
Meat extractives	Whole-grain cereals—such as cooked whole wheat and wheat biscuits	
Meat soups	Whole-grain bread—such as whole wheat and graham bread	

* Contain practically no purine as served.

(carrots, beets, string beans, or small serving of vegetable in column 2 of list), salad, bread, butter, milk or tea, choice of dessert.

Non-alcoholic beverages and fruit juices often encourage the maintenance of an adequate daily intake of fluid.

Drugs.—Cinchophen (atophan) and neocinchophen (toly-sin) increase the excretion of uric acid and are beneficial in the treatment of chronic gout. These drugs rarely may cause acute yellow atrophy of the liver, but their value greatly overshadows this remote possibility and Hench (1935) advocated their general use in gouty individuals. The method of administration for either drug is an oral dose of 0.5 Gm. ($7\frac{1}{2}$ grains) three times daily for three days repeated each fortnight. Neocinchophen is perhaps less toxic than cinchophen

and less likely to cause gastro-intestinal disturbances. Acetyl salicylic acid, 0.3 Gm. (5 grains) given every three hours, often controls mild discomforts caused by gout. Colchicine has no apparent value in the treatment of chronic gout.

Mercurial diuretics should never be used in a gouty individual. Price reported five cases in which salyrgan was administered for relief of dropsy, after which acute gout developed, with a fatal outcome in several cases.

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OBESITY

OBESITY is the most prevalent of the metabolic diseases. It has been estimated that one of every five adults in the United States is overweight. The untoward effect which obesity, as a

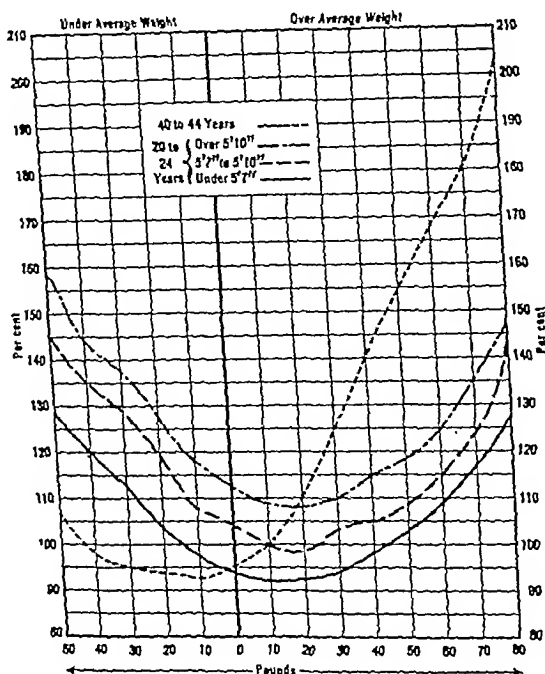


Fig. 81.—The relationship which body weight and height bears to the mortality rate is presented (Medico-Actuarial Mortality Investigation). The mortality rate of persons between forty and forty-four years of age is lowest when the weight is 10 pounds under the average weight and it rises steadily as the weight increases above this level until, at 80 pounds above the average weight, it is over twice the normal rate. Contrasted with this is the lowest mortality rate for persons between twenty and twenty-four years of age, when the body weight exceeds the average weight by 10 to 20 pounds.

complication, has upon the mortality rate of other diseases has long been known; but, judging from the attention it receives in contrast to acute infections, this influence is not fully appreciated.

Obesity is a national problem and one which deserves a prominent place on public health programs.

An individual is obese when fat is deposited throughout the body in excess of body needs. Excessive fat assumes pathologic proportions when it interferes with the function of organs. A slight deposit of body fat may cause no inconvenience, and may even be desirable in the maintenance of good nutrition of body tissues; but mortality statistics show that overweight adults have a shortened life expectancy (Fig. 81). Insurance companies are well aware of this fact and consider obese applicants much less desirable risks than those of normal weight.

ETIOLOGY

There are a number of factors which bear on the development of obesity. It is now recognized that the intake and absorption of fuel in excess of that needed for growth, repair, and the expenditure of energy results in deposition of fat, and that the mathematical principle so expressed applies to any form of obesity.¹ *Heredity*, either by inheritance of a vigorous gastro-intestinal tract, abnormal irritability in centers of the diencephalon where feelings of hunger and satiety originate,² or by a tendency to glandular deficiencies, plays an important part in many patients. *Environmental influences*, such as the tendency for gourmandizing in certain families, the lack of energy expenditure concomitant with a sedentary occupation, or dictated by inclination or by physical impairment, are important. In certain races obesity tends to be especially prevalent. This is true of Hebrews, Turks, Southern Italians and some African tribes. Obesity is more common in women than in men, probably because of less physical activity. It tends also to increase with age to the seventh decade, and especially increases in women at the menopause. Men tend to acquire excess fat in "the forties."

Two distinct types of obesity are recognized, the *exogenous* and the *endogenous*. Mixed endogenous and exogenous obesities occur and account for enormous degrees of overweight.

TABLE I
CHARACTERISTICS OF THE DIFFERENT TYPES OF OBESITY

Simple or exogenous.	Endogenous.			
	Thyroid insufficiency.	Gonadal insufficiency.	Pituitary.	
			Frölich's syndrome (juvenile).	Adult hypopituitarism.
Normal endocrine reactions. Generalized distribution of adipose tissue. Excessive perspiration. Sensitive to heat. Dyspnea on exertion. Swelling of ankles in later stages.	Cold extremities. Sensitive to cold. Subnormal basal metabolic rate. Dry, thick skin. Lack of perspiration. Coarse and falling hair. Slow speech. Physical sluggishness. Deposits of fat over clavicles, and on ankles, especially about malleoli. Hypercholesterolemia.	Lack of development of secondary sex characteristics. Amenorrhea or oligomenorrhea. Sexual frigidity. Fat deposits predominate about hips and thighs.	Genitalia underdeveloped. Knock knees. Female body conformity. Female distribution of hair. Fat deposits, especially about face, neck, chest and abdomen.	Genital hypoplasia. Heavy fat deposits in face, chest, upper arms, abdomen and thighs. The fat has a tendency to form hanging folds. Hands and feet escape fat deposits and appear disproportionately small.
				Cushing's syndrome.* Marked hirsutism. Hypertension. Diabetes mellitus. Elevated basal metabolic rate. Osteoporosis. Deposits of fat in the face, breasts, abdomen and interscapular region giving the buffalo-like appearance. Purplish striae atrophilicæ.

* This syndrome may be duplicated in patients having adenomata of the adrenal cortex.

In Table 1 is shown a detailed classification of the features of the different types of obesity.

Exogenous Obesity.—This occurs when overweight develops purely because the patient's food intake exceeds the *normal* requirement to maintain the weight at the *normal* level. After satisfying the normal basal needs of the body, the normal specific dynamic action requirement, and the exercise re-

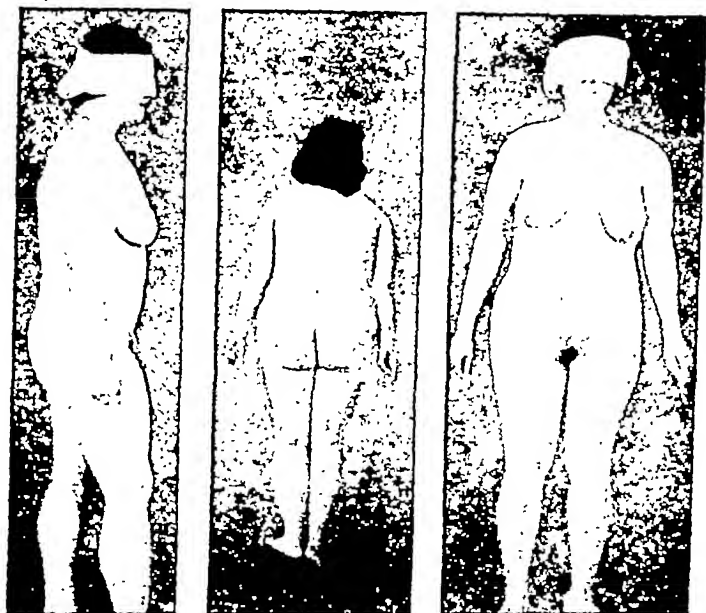


Fig. 82.—Simple obesity. E. F., nineteen years old, weighed 213 pounds when first seen and had reduced to 182 pounds when this picture was taken. Note the generalized distribution of adipose tissue extending on the arms to the wrists and on the legs to the ankles.

quirement, there is excess nourishment which is deposited as fat. It is by far the most common type of obesity.

This type of obesity is illustrated by the case of E. F., aged nineteen years, who came to the hospital because her obesity had prevented her from entering a training school for nurses. Neither of her parents was overweight, although her mother had gained some weight at the menopause. Her weight was 213 pounds (96.8 Kg.) and her height 5 feet, 6 inches

(167.6 cm.). She had been overweight since about ten years of age. Her sexual development had been normal, menses having begun at the age of thirteen years and having been of normal regular appearance since. Her basal metabolic rate was minus 1 per cent and her blood pressure was 105 mm. Hg systolic and 70 mm. diastolic. The fat was generally distributed (Fig. 82), extending on the extremities to the wrists and ankles.

A diet containing 1600 calories was prescribed and thyroid substance, $\frac{1}{2}$ grain, was given twice daily. After two weeks of this regimen her pulse rate had risen from 80 to 92 per minute, and her weight had decreased to 199 pounds (90.4 Kg.), a loss of 14 pounds (6.3 Kg.). The thyroid substance was discontinued without interrupting the loss of weight. After three months her weight was 182 pounds (82.0 Kg.), pulse 84 per minute, and blood pressure 125 mm. Hg systolic and 65 mm. diastolic. Moderate exercise was advised in addition to her usual activity of assisting with house work. She received no diuretics. A weight of about 155 pounds (65.9 Kg.), which is 15 per cent above the average for her height and age, would be satisfactory for this patient.

Endogenous Obesity.—Endogenous obesity is attributable to some single, or to a combination of endocrine disturbances. The need for food to maintain a normal weight is reduced by one or a combination of the following: (1) an abnormally low basal need, (2) a lowered specific dynamic action of food, and (3) the reduction of physical activity. A normal intake of food under such conditions obviously exceeds that necessary to maintain a constant and normal weight. Obesity results.

Endocrine obesities may be subdivided into several groups according to the particular gland predominantly involved. Disturbance of more than one endocrine gland is the rule, and the varying degree of involvement of the different glands presents many individual variations of obesity.

The **thyroid type** of endocrine obesity is due, chiefly, to undersecretion of the thyroid gland. Patients suffering from this type of obesity, which is rarely of extreme degree, have short stubby hands and feet, with a tendency to deposits of fat in pads above the clavicles and the ankles. Other accompanying features help to identify this type, notably the thick,

dry skin; dry, coarse hair, which falls out easily; thinning of outer portion of the eyebrows; slow speech; elevated blood cholesterol; and lowered basal metabolic rate.

The following case is illustrative: M. S., aged sixty-nine years, complained of indefinite aches and pains. She has been overweight for at least twenty years with an increasing tendency to inactivity. She seldom leaves home and she takes little interest in outside affairs. Her hair is dry and coarse; her skin is thick with coarse wrinkles in her face. Her breasts and abdomen are pendulous, and she has pads of fat above the clavicles and on the ankles (Fig. 83). There is no pitting of the swelling, either over the malleoli or on



Fig. 83.—Thyroid obesity. M. S. Aged sixty-seven years. Note the pads of fat about the malleoli and over the dorsum of the feet. The swelling does not pit on pressure.

the dorsum of either foot. She is 4 feet 11½ inches tall (151.1 cm.) and weighs 165 pounds (75 Kg.). Contrary to the rule she has an arterial hypertension, 175 mm. Hg systolic and 90 mm. diastolic, and her pulse varies from 80 to 90 per minute. She also has a severe Addisonian anemia, which has been irregularly controlled by means of liver extract. She has been uncooperative, and in consequence the result obtained is not satisfactory.

The continuous use of thyroid substance is, of course, advisable. It should be given in sufficiently large amounts to maintain as nearly a normal basal metabolic rate as possible, using the pulse rate, nervous symptoms and clinical response as guides. It is not always possible to keep the basal metabolic rate up to normal without untoward nervous symptoms; but the other features of the disease are readily controlled on

a dosage less than that which provokes symptoms. A good practice is to start with $\frac{1}{2}$ grain morning and noon, gradually increasing each dose until a satisfactory clinical response is obtained.

The gonadal type of obesity is attributed to insufficient testicular secretion in men and to insufficient ovarian activity in women. It is particularly common in women at the menopause, natural or artificial after removal of the ovaries.



Fig. 84.—Gonadal obesity. Note the excessive deposits of fat about the hips and thighs. (Courtesy of Dr. Jacob Hoffman.)

Eunuchs and men with undescended testes frequently become obese. The characteristics of this type of obesity are the deposits of adipose tissue in the abdomen, hips and thighs, especially in the trochanteric regions.

Mrs. G. M. illustrates the gonadal type of obesity. She consulted her physician because of "hot flashes" and nervousness at the age of thirty-eight years. These symptoms had begun about six months previously and had been growing worse. Menses had not occurred for the preceding three months and had been somewhat irregular for several months before that time. There had been some evidence of ovarian deficiency all her adult life in that, although she was married and had one child, she had never had any interest in sex

life. She had noted that she had grown very much larger about the hips and thighs when she was about thirty-two years of age. On examination she appeared quite normal except for the marked deposits of fat on the hips and thighs, very similar to the patient illustrated in Fig. 84. She was given theelin, 2000 units intramuscularly, at three- or four-day intervals with complete relief of symptoms, but without effect on the fat deposits. Her height was 5 feet 2 inches (151.4 cm.) and her weight 155 pounds (70.4 Kg.). She was given a diet containing 1500 calories, without extra nourishments. She had been in the habit of using sweets freely. Her weight gradually decreased until now, at the age of forty years, it is 128 pounds (58.2 Kg.). The nervousness and "hot flashes" have grown much less frequent also and she no longer requires theelin for their control. Her menses have not returned.

Pituitary obesity is due to deficiency in secretion of the pituitary gland primarily, or is secondary to abnormalities in the hypothalamic area. It assumes one of three types: (1) *dystrophia adiposogenitalis* in the young (Fröhlich's syndrome), and the adult form of hypopituitarism, (2) the Laurence-Moon-Biedl syndrome, and (3) pituitary basophilism (Cushing's syndrome).

1. *Dystrophia adiposogenitalis* is most readily recognized in children before puberty, although it may occur later in life. The fat deposits are chiefly in the face, neck, across the chest and abdomen, and on the upper arms and upper thighs. The lower arms and hands, and the lower legs and feet, are strikingly spared and by comparison appear thin. Before puberty, the genitalia are underdeveloped, and at a later age the sex characteristics are of the female type. The beard is scant or there is none at all; there may be gynecomastia; the pubic hair distribution is of the female type; there is a tendency to knock knees; and the fingers are tapered.

Case L. C. (Fig. 85) illustrates a typical Fröhlich's syndrome in a boy aged fourteen years who came to the hospital because of a palmar abscess which was drained. He had noted an increase in weight since he was ten years of age. He had had rheumatic fever twice, once at nine years and again at thirteen years. He had also had measles, chicken pox, mumps, and had undergone tonsillectomy and adenoidectomy at seven years. He had no complaints referable to his obesity except slight dyspnea on moderate exertion. His weight was 187 pounds (85 Kg.); he was found to have a blood pressure of 130 mm. Hg systolic and 78 mm. diastolic, and excessive fat deposits in his face, neck, breasts and abdomen. The arms above the elbows were disproportionately fat, the fingers were tapered, and he had some tendency to knock knees. The external genitalia were infantile. The basal metabolic rate was minus 13 per cent; the Wassermann reaction and urinalyses were negative. He remained in the hospital for only a short period. He was given a diet containing protein, 90 Gm.; carbohydrate, 120 Gm., and fat, 73 Gm. (1500 calories).

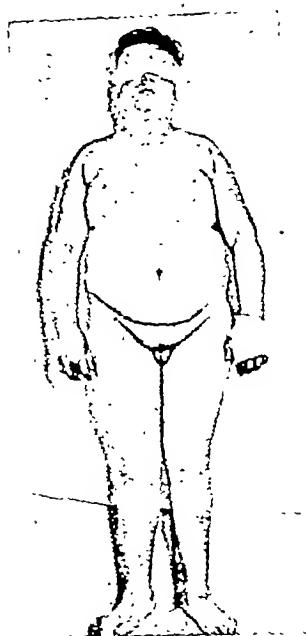


Fig. 85.—Pituitary obesity (Fröhlich's syndrome). L. C., fourteen years old, first noted excessive weight when ten years of age. Weight at the time of this picture 187 pounds. Note the full face, folds of fat on the torso, and small genitalia. The tapering fingers do not show well in this picture.

2. The "Laurence-Moon-Biedl syndrome" is similar to Fröhlich's syndrome but is accompanied by developmental anomalies such as retinitis pigmentosa, syndactylism and mental deficiency.

3. The obesity associated with pituitary basophilism (Cushing's syndrome³) is the result of an adenomatous growth of the basophil cells of the pituitary body, which by its pressure is believed to reduce the secretion of the remainder of the pituitary gland and obesity ensues. Oversecretion of the basophil cells is believed to account for the development of secondary sexual characteristics of the masculine type. The hirsutism and deepening of the voice are prominent features. Diabetes develops and hypertension occurs, probably due to secondary stimulation of the adrenals. Osteoporosis also occurs, particularly in the vertebrae, allowing the shoulders to arch forward. There is fat deposition in the face, the neck,

in the interscapular area and in the breasts and abdomen. The full face, arched shoulders, with the fat pad on the back between the shoulders, give the patient a buffalo-like appearance. Bluish striae atrophicae are marked in the skin of the abdomen and arms. Fig. 86, taken from Cushing's original



Fig. 86.—Pituitary obesity. Basophilism (Cushing's Disease). Cushing's case of "dyspituitarism": twenty years later. Note the hirsutism, the increasing rounding of the shoulders, the pendulous abdomen, and the striae atrophicae. (Archives of Internal Medicine, Vol. 51, No. 4, April, 1933.)

article, illustrates this type. The obesity is overshadowed in importance by the other features of the disease. The treatment recommended is roentgenotherapy of the pituitary gland, or surgery. Fortunately the disease is rare.

Adiposis Dolorosa (Dercum's Disease).—The cause of

this type of obesity is unknown. The adipose tissue is deposited as small or large nodules which are painful. The disease is frequently accompanied by mental disturbances.

SYMPTOMS

Dyspnea is the most common symptom of obesity. Mechanical interference with the free movement of the limbs is present in severe cases and skin irritation occurs where fat folds cause approximation of the skin surfaces. The obesity associated with endocrine disturbances is accompanied by the symptoms of the respective endocrine deficiency.

The complications of obesity, which result in advanced cases, give rise to many symptoms. Elevated blood pressure and its attendant cardiovascular disease contributes the special symptoms of these conditions. Cerebral hemorrhage, angina pectoris, and kidney insufficiency are common. Diabetes mellitus develops from ten to twenty times more frequently in obese than in normal people.⁴ Herniae, skin infections, carbuncles, eczema, varicosities, and joint disorders, particularly of the knees and feet, are commonly associated with obesity.

TREATMENT

In the treatment of obesity the needs of each individual must be duly considered. Those who have a predisposition to overweight, either through heredity, race, or occupation, should exert every effort to prevent obesity. Its correction is much more difficult than its prevention. For persons under thirty years of age, and those who suffer from tuberculosis or are exposed to it, and those suffering from hyperinsulinism, a moderate increase in weight, 5 to 10 per cent, above the average or standard weight is desirable. Individuals who have heart disease, gout, or diabetes, should remain 5 to 10 per cent under the average weight.

Diet.—Having decided that weight reduction is necessary, the next step is the computation of the *caloric value* of the diet. At rest, 25 calories per kilogram are needed for the maintenance of a constant body weight. A diet containing 20 calories or even less per kilogram of body weight may be necessary to secure a reduction in weight. To maintain nitrogen balance, 1 Gm. of *protein* per kilogram of body weight is

required. For an adult, therefore, the protein content of the diet will seldom be less than 60 to 70 Gm. In children, relatively more is needed (3-4 Gm. per Kilo). *Carbohydrate* should make up about a third of the total calories. *Fat* then constitutes the remainder not provided for by the protein and carbohydrate. A sample diet may be computed in the following manner:

For a man of thirty-five years, whose height is 5 feet 7 inches (170.18 cm.), we learn from the height-weight-age tables that the average weight for his age, height and sex is 150 pounds (68.18 Kg.). If we then compute the caloric value of his diet according to the desired weight, allowing 20 calories per kilogram, we find that he may be allowed 1360 calories. This may be supplied by protein 68 Gm., carbohydrate 112 Gm. and fat 70 Gm. (1350 calories).

The initial diet is a trial diet, further restrictions being made if weight loss does not occur within a week. It is frequently necessary to reduce a patient's diet markedly below the calculated maintenance level, especially if he is at rest. Under such conditions a diet containing 1100 calories for a patient of 180 pounds (81.8 Kg.) is not uncommon.

The dietary list need not be a complicated affair. The diet lists of different caloric content outlined by Duncan (Table 2)⁹ fulfills, for practical purposes, all the requirements for the dietary prescription when accompanied by a list of the carbohydrate content of vegetables and fruits (see page 1512). Foods of large bulk and low carbohydrate value should predominate. They furnish considerable satiety value without greatly adding to the caloric intake.

It will be observed from what has been presented above that the fats, which yield 9 calories per Gm., are restricted. Sweets should be interdicted entirely, and saccharin may be used as a substitute for sugar in coffee and tea. It must be remembered that, when the consideration of alcoholic drinks arises, alcohol furnishes 7 calories per Gm., almost as much as fat. Strang and Evans⁵ have advocated very low caloric diets—500 calories—and apparently avoided the symptoms, which might be expected with such low diets, by giving large quantities of supplementary vitamins and minerals. Vitamin B is available in yeast tablets and vitamins A and D in cod liver oil or halibut liver oil concentrates fortified with viosterol.

Wilder⁶ suggests that Kalak water or Tyrode's solution without glucose may be given to insure adequate minerals.

Grafe⁷ calls attention to the fact that certain patients carry much of their excessive weight in the form of retained water in the absence of visible edema. Salt should therefore be restricted to that contained in the food only, and water restricted to that necessary to alleviate thirst, usually not exceeding 1500 cc. daily.

Exercise.—Exercise is a valuable adjunct to the reduction diet for those for whom there is no contraindication. Walking on the level is suitable for most ambulatory patients. Those without cardiovascular complications may take part in gymnastics, golf, tennis, swimming, horseback riding, or rowing. For those who cannot exercise actively, massage and passive movements may be worth while. Douthwaite⁸ has emphasized the value of special exercises of the abdominal muscles for abdominal obesity. This can be practiced at frequent intervals during the day.

Drugs.—Thyroid substance may be used in obstinate cases even in the absence of an insufficiency of the thyroid secretion. It is, of course, essential in the treatment of the thyroid deficiency type of obesity. Small doses should be used at first, beginning with $\frac{1}{4}$ to $\frac{1}{2}$ grain of desiccated thyroid gland. The amount is gradually raised to 2 or 3 grains daily.

Patients should be warned against the use of commercially advertised nostrums, many of which contain thyroid substance. Dinitrophenol should not be used because of the danger of hepatitis, granulopenia and other complications. Patients with salt and water retention are greatly benefited by diuretics. Mercupurin, 2 cc., given intramuscularly at three-day intervals for three doses frequently causes an enormous diuresis.

PITFALLS AND CAUSES OF FAILURE

It should be borne in mind that a very rapid reduction in weight may cause the individual to appear haggard. A slow reduction allows the skin to adjust itself to the lessened bulk. Also, when the reduction is too rapid considerable weakness may ensue. In event of severe autonomic reactions, such as weakness, sweating, palpitation, or faintness, the patient may be so frightened that he refuses to cooperate. A loss of 1 to 2

pounds per week is sufficient. A practical plan is to have the patient take a glass of skimmed milk or some article of food between meals—in the midmorning, midafternoon, and at bedtime. This tends to prevent the development of a great appetite so common when the meals are spaced far apart.

An uncontrolled anemia with its attendant weakness may cause the patient to eat excessive amounts of food in an effort to keep up his strength. In a carefully studied case this will be identified and treated.

SUMMARY

1. Obesity causes a definite reduction in longevity. Its prevalence makes it a subject of extreme importance. 2. Food in excess of the requirement to keep the body weight constant is the fundamental cause of obesity. 3. Obesity is divided into two classes, exogenous and endogenous. The latter is subdivided according to the characteristics of the respective glandular disturbances—thyroid, ovary, testes, pituitary and adrenal. 4. Case reports of the various types of obesity have been given. 5. The treatment by restriction of the diet, by thyroid medication and diuretics, and by exercise, has been discussed.

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MALNUTRITION

DEFINITION

IN order properly to reach an understanding of a subject it is necessary to define it, and so that we may limit the discussion to pertinent matters relating to malnutrition, it is important to present a concise interpretation of the term. Malnutrition is obviously a qualified form of nutrition, so that the first consideration is to determine what constitutes nutrition itself. Graham Lusk¹ has defined nutrition as "the sum of the processes concerned in the growth, maintenance, and repair of the living body as a whole or of its constituent parts." Since growth, maintenance, and repair are functions of cells, it seems proper to conclude that their sum is similarly a function and thus that nutrition is a function of the body.

Functions are in themselves normal to an organ as a unit, or to the body as a whole, but further than that they may be well or poorly performed depending upon the efficiency of the organ or body of which they are a part. Cathcart² has defined good nutrition as "the state of well-being which characterizes the individual who is physically and psychologically sound," and the opposite of this would appear to be malnutrition. Herein lies a major difficulty, for there arises the necessity of determining whether or not an individual is sound. Standards of physical and psychological fitness are difficult to set up and must be made with regard to intended purpose in the individual case. Thus in the Victorian era physical soundness was based upon the economic need for muscular bodies able to perform heavy labor; today, the requirements of technological employment are for other qualities—quickness, rapid reaction time, and muscular coordination rather than strength alone. Psycho-

logical soundness can no longer be evaluated in terms of the slow turning of a furrow, but must now be related to the insatiable demand of a moving assembly line that is unresponsive to the slackening mind or the hand of fatigue.

The nutritional state, as a function of the body, is good or bad in respect to the economic and social environment of the individual in its demands upon him to fill an active and useful place as a member of society. Good nutrition exists in individuals who are physically and mentally able to meet these demands, whether they be students requiring athletic and academic fitness, mechanics requiring muscular coordination, or clerks called upon to perform mathematical calculations in sedentary occupations. The criteria for the fitness of each group may therefore vary, but the fundamental principles for the development of those criteria nevertheless apply to each.

ASSESSMENT OF THE STATE OF NUTRITION

The physician is the final judge of the nutritional state of the patient. His criteria are derived from past experience and are subject to his personality, training, and judgment. His immediate judgment is a synthesis of impressions gained by examination of the individual and his *previous* conception of normal nutrition. Three factors play parts in the evaluation of a patient's nutrition: (1) the conception of the normal, (2) the physician, and (3) the immediate examination.

First, in regard to the *conception of normal* from past experience, should the physician accept as the individual normal the average of the group from which his impressions have been gained? Admittedly this is the usual practice, but much evidence has accumulated to indicate that it is an improper procedure and that he should consider the average of the group as far below the potential, and therefore optimal, nutritional level of the individual. Health authorities conclude that even in the high income groups (one generally accepted standard for group comparison) definite improvement is obtainable by slight changes in the diet. This is but one of the factors that condition nutrition. Similarly, from the experimental laboratory comes evidence, based on statistics relating to animal growth and to breeding, that an appreciable gap exists between what constitutes maintenance nutrition and the optimal state.

It would therefore seem proper to revise the present conception of the normal as derived from past group experience to the criterion of optimal realization of individual potentialities.

Disregarding for the purpose of this discussion the second factor in evaluation, we are faced with the third factor, or *the immediate examination*. This is gained in practice by assessing the physical state supplemented by information about the subjective well-being.

We find, written into the tissues of the physical state, a record of the past as well as the present, and we must consider the nutritional state in terms of a whole, encompassing all previous influences as well as those of the present. As an example, the rachitic deformities following a vitamin D deficiency in childhood or the corneal opacities of xerophthalmia from the war years are apparent in the adult who yet may be adequately or even well nourished in respect to the present. Thus there is a functional background upon which we find a recent nutritional state superimposed. The latter is so evanescent an appearance at best that even the psychological events of fear, anger, depression, or happiness may rapidly alter it. It is therefore essential that we distinguish between these two aspects of the impression, for from the one we learn of the adequacy of the processes contributing to the nutrition during the formative years, and from the other those of the immediate past, each important and requiring correlation in respect to functional well-being.

Total Nutrition.—Evidence of the total nutritional state is best found in the *bony structure*, for this carries a more or less permanent record of the adequacy of the developmental years in supplying the essentials for its normal growth, dependent as it is upon mineral and vitamin supply as well as balanced functional use. The *teeth* similarly participate in this record, and the presence or absence of caries, the loss of enamel, and the spacing, all may be used in the judgment of the total nutritional state. *Posture* is a third acceptable criterion, for it reflects the tone of the muscles throughout the past. Finally, *total stature* must be considered, although this is a debatable point in regard to the evaluation of a given individual. It may be assumed that height is to a certain extent dependent upon adequate nutrition as well as hereditary

characteristics. Certainly as Aykroyd³ has shown in India it is a function of nutrition when correlated by group statistics.

Recent Nutrition.—In contrast to these evidences of the past, we may find the record of the recent nutritional state in the *soft tissues*. A comparison of total flesh to bone is essential, and here it is necessary to distinguish between the tissues of high and low biological activity, the muscles and the fat deposits. The fat individual is not necessarily a well-nourished one, and in point of fact is usually the opposite, with flabby muscles. Muscle tone is one of the best criteria for the evaluation of the recent nutritional state, and should be sought for locally by a dynamometer test and generally by posture.

The second place to search for evidence of malnutrition is in *the skin*. Here we may find conditions varying from outright pellagra and scurvy (absolute deficiency disease), to mild malnutrition as evidenced by loss of elasticity, impetiginous areas, coarsening, and chapping of the lips and hands.

The third source of information is in *the blood* where there is a rich record, not only of the adequacy of supply, but also of utilization. As a single example consider the common hypochromic anemia of the menopausal years, which must be evaluated in terms of iron intake and excretion; *i.e.* the efficiency of its absorption and the factors that control that process (the gastro-intestinal pH, intestinal motility, and the functional state of the mucous membrane), and the iron-calcium-phosphorus ratio in the diet. After absorption of this one element, its utilization within the body is to be considered.

This is a brief evaluation of nutrition and the methods for the assessment of this functional state of the body, in order that it may be judged good or bad as the case may be.

FACTORS CONDITIONING NUTRITION

Inquiring into the many factors that have to do with the conditioning of the functional state of nutrition reveals an exceedingly complex situation. One element may compensate for another, whereas its absence would lead to malnutrition. For example, there is the classical picture of the development of rickets in a child during the winter months because of decreased exposure to sunlight despite no appreciable change in the vitamin D intake, or the appearance of the skin lesions of

pellagra in the individual on a non-pellagra producing diet because of gastro-intestinal disease. We may well expect that as a result of this complexity there will be a diversity of active factors, each effective in its own way and all serving to produce a composite picture that will be reflected in the final nutritional state of the individual:

The first of these is *physical environment*. This is to a large extent dependent upon the economic state, though not necessarily so. Of importance are the amount of fresh air available, housing conditions, exercise, and adequate rest periods. Geographically, the physical environment varies over the face of the habitable portion of the earth, and climatic conditions are influential in the production of the nutritional state. Secondly, there is the *psychological environment*. Happiness and contentment of mind are often more important for good nutrition than the provision of an excess of one or another of the constituents of the diet. The mental characteristics of the individual and of his family play a large part in his fitness. Third, *disease*, for obvious reasons, conditions nutrition. Fourth are the *individual requirements*. One person may need more sleep, more exercise, or more laughter than his neighbor. The fifth factor is *food*.

Nutrition is frequently considered only in respect to food intake. This makes for a confusion in fundamental terms, since a person may be well fed and yet be poorly nourished. It would be more correct to call food nutrition "alimentation," and the efficiency with which the nutrient is used as a factor in the production of good or bad nutrition of the body.

The foregoing are in brief some of the factors governing nutrition. Each is important and must be carefully evaluated in respect to the individual under consideration. However, in order to narrow the scope of the present discussion, further consideration will be given to but one of these, alimentation, and the problem presented by malnutrition due to deficiency in respect to it, keeping in mind that the other factors will modify the effect of alimentation in different individuals.

ALIMENTATION

The requirements for food are qualitatively the same throughout life; quantitatively, however, there is a large varia-

tion which is dependent upon many factors. Thus it is apparent that *age* will be an essential consideration in the quantitative consideration of alimentation, the child being biologically different from the adult in the prime of life and these two far removed from the senescent. In the young there is the factor of growth; growth is extremely rapid during the first three years, this is followed by a period of steady but relatively slow gain until the age of puberty, when there is again a period of rapid growth that increases the demand not only for total food intake, but also for specific substances. During this period of life, also, there are the specific diseases natural to it: the exanthemata, not usually met with in later years but each placing a severe burden upon the child which must be met by changes in alimentation if good nutrition is to be maintained. Similarly there are emotional factors of importance, particularly at puberty, which are suddenly presented to the organism that is not prepared by experience and training for their solution. The resultant effect upon alimentary requirements is marked and sufficient to demand consideration from the medical examiner. Old age, in contradistinction to youth, is a period requiring quantitative changes in alimentary habits, dependent upon degenerative changes affecting the intestinal tract, a lowered rate of metabolism, and an inability to store essential food factors, so that there arises the necessity for an increased daily intake of those substances.

A second element affecting the alimentary requirements is the *occupation* of the individual. This is chiefly related to the requirements resulting from the increased metabolism of work. Thus it is generally accepted that the average requirement at rest is approximately 1500 calories, and yet the same individual, if working as a laborer, may need as much as 4500 or 5000 calories. It is conceivable that the present-day driver of a freight truck passing long hours in the night at the wheel will have a much higher requirement for vitamin A in order to have optimal night vision than the farm worker who yet may utilize an equal amount of energy at his task. Thus it would appear that the occupation may bring about changes in alimentation, not only in respect to the total requirements, but also in the individual components of the diet.

The same is true of the third factor, *environment*, and by

this one thinks chiefly of climate. Generally speaking, the average individual varies his dietary intake with the seasons, increasing the liquid and cold foods with the hot seasons of the year, and the heavier substances in the winter. A more specific example of this factor in maintaining alimentary good nutrition is the increased need for salt in individuals occupied in work that exposes them to great heat, as was the case of the men who erected Boulder Dam.

The fourth and final factor of importance in quantitative alimentation is that of the *variability of the individual*, not only in regard to the whole, but perhaps of more importance to the individual components of the diet. This individual requirement varies to a large extent according to the state of nutrition which has preceded the immediate period under consideration, so that the general health and physical condition assumes a large share in the control of the needed food intake. Inherited characteristics are of some importance, though this factor exists chiefly in childhood when the infant must make up for the deficiencies of storage and supply that developed during embryonal life. A mother inadequately supplied with the various essential substances during gestation, although nature may sacrifice her for the benefit of the child, nevertheless passes on to that child the potential need for a greatly increased intake of those substances immediately after birth. An excellent example of this is the development of secondary anemia of a rather severe grade during the first and second years in those children born of mothers suffering from an iron-deficiency anemia during pregnancy.

So much for the general considerations of the factors that will influence alimentary requirements in the larger and more general categories. In respect to the nutritional state of the individual, we find that there is a group of balances that must be considered as bearing upon the control of adequate alimentary nutrition, each of which is important. They consist in (1) an adequate intake; (2) the proper absorption of the food; and (3) the utilization and storage of the absorbed substances.

FOOD INTAKE

It is axiomatic that there must be an adequate supply of food components in the diet. This means sufficient biologi-

cally-active *protein* to insure body cell maintenance and growth. There are ten nutritionally essential amino acids and these occur widely in nature, both in vegetable and animal products. The latter would appear to contain them in a more utilizable form so far as the human is concerned, and meat and dairy products should therefore be included in all dietaries. The amount of energy-producing substances, principally *carbohydrates* and *fats*, is dependent chiefly on the caloric requirements of the individual. There is evidence that for rats and presumably for man, some of the fatty acids are essential for growth and the maintenance of life.⁴ Normally, the average caloric requirement for an adult male is between 2000 and 3000 calories for a moderately active life, with a variation from 1500 for bed rest to 5000 or more for growth and maximum activity.

The third component of the diet, *minerals*, is equally vital. Thirty-seven different minerals have thus far been isolated from the body; some of them are present only in the minutest trace, having as yet little known biological activity and probably only occurring as they happen to be present in the other substances in the diet. However, certain minerals are essential to body nutrition and these may be briefly enumerated: iron, calcium, iodine, sodium, magnesium, potassium, copper, phosphorus, zinc, and cobalt.

Finally there are the *vitamins*, of which some twenty-two are known. Fourteen appear to be essential for animal growth, and the human need is probably closely related, although definite proof of this is lacking. The human requirement for vitamins is given in the Tabulation.

TABULATION

VITAMINS: ADEQUATE FOR HEALTH TO OPTIMUM LEVELS

Vitamin.	Child.	Adult.	Pregnancy.	Units.
A....	2000-8000	3000-6000	6000-10,000	Sherman
B complex. ...	200-600	400-900	900-1200	Sherman
C....	80-100	60-100	100-200	Sherman
D.	300-1000	140	800	International
G.	400-800	400-600	600-800	Sherman
Thiamin chloride ..	100	500	1000	International

Factors Adversely Affecting the Intake.—Certain conditions must be considered as adversely affecting the intake of food. First in importance is *ignorance*, and this we find exists not only among the laity, rich and poor alike, since wealth is not a guarantor of either intelligence or good nutrition; but often in the medical profession also. Second are the conditions that result from the *economic situation* of the individual. Both of these factors play parts in the present consumption of highly refined cereals, canned foods, and the following of food fads and fancies. A third cause operates chiefly in those individuals who are following diets prescribed by physicians for the control of *disease processes*: peptic ulcer, renal disease, hypertension, diabetes mellitus and allergic states. Here alimentary malnutrition develops because of the lack of one or more essential substances in the diet or because treatment results in deficient absorption of some needed material.

Physical conditions may affect adversely the food intake, such as nausea, sore mouth, imperfections and absence of the teeth, dysphagia and anorexia. Anorexia is of special interest in that the appetite seems to be dependent to a large extent upon the intake of a proper quantity of vitamins in the diet. Hence a vicious circle may be created in which loss of appetite leads to a decreased intake of those substances which will induce the desire for food. Closely related to the physical conditions regulating the food intake are the emotional factors. Fear, anxiety, and anger play important rôles and may produce sufficient interference with alimentation to cause what is apparently an organic malnutrition. Attention has recently been brought to the fact that many of the cases hitherto considered true Simmonds' disease due to a pituitary insufficiency are examples of anorexia nervosa—malnutrition of a severe degree dependent upon anorexia due to some emotional conflict that the patient has been unable to solve.⁵ Finally, alcohol is a substance that seriously alters food consumption, affecting as it does not only the desire to eat, but also the absorption of food in the intestinal tract. The pellagra found in the northern states is often an excellent illustration of this effect of alcohol with resultant malnutrition.

ABSORPTION

Having assured an adequate intake of food substances, it is next necessary to inquire into their absorption from the intestinal tract and the conditions that lead to the impairment of that process. Obviously this has to do primarily with the integrity of the intestinal tract and with the satisfactory carrying out of its physiologic activity. Any disturbance of this activity may have a deleterious effect upon nutrition because of inadequate alimentation.

The *digestive secretions* are the first substances that may be considered, especially the gastric, pancreatic and biliary juices. One aspect of achlorhydria has been already suggested, that of hereditary achlorhydria. The absence of hydrochloric acid is exceedingly important, particularly in respect to the absorption of iron, calcium, and vitamins B and C. Iron and calcium form insoluble phosphate salts in an alkaline medium so that the changes in the intestinal reaction consequent to an achlorhydria result in their inadequate absorption and an increased loss by bowel (the hypochromic anemia of the elderly is partially conditioned by this factor, as is also senile osteoporosis). One interesting aspect of the problem is the relation of vitamin B to the gastric secretion of acid; thiamin chloride is apparently poorly absorbed in its absence and also, experimentally, rats develop achlorhydria on a thiamin chloride deficient dietary. Although there has been no definite proof as yet developed that this applies to the human, nevertheless it is an inviting path upon which to speculate as to its possible significance in the large percentage of achlorhydrias that occur after fifty years of age in the general population. A decrease in the pancreatic secretion may result from either atrophy of the gland secondary to chronic pancreatitis, from obstruction to the ductal system by lithiasis, inflammation with stricture, or by new growths. The improper digestion of fats, and to a certain extent carbohydrates, in the absence of or decreased amount of pancreatic enzymes brings about a deficiency in their absorption; rapid emaciation is the usual result and the added factor of diarrhea that often develops, non-tropical sprue, hastens the development of malnutrition in respect to other essential foods.

Biliary insufficiency similarly has an effect upon the fats of the diet, their improper digestion being due to the need for the bile salts to form soluble absorbable products. The exclusion of bile from the intestinal tract results from biliary fistulae and obstruction to the common duct by stone, stricture, or by carcinoma. In any case the result is the same no matter what the cause so far as alimentation is concerned. In this respect it is important to realize that two of the essential vitamins (A and K) are fat soluble, and hence the deficiency consequent upon the deprivation of the body of these will inevitably develop.

The second group of factors changing the physiology of the intestinal tract are those resulting from what might be called *gross anatomical lesions* of its various parts. These may vary from obstruction due to carcinoma or stricture; to atrophy of one or another of the cellular constituents of the mucous membrane; or fistulae, either between sections of the bowel or to the surface of the body. The mechanism of obstruction is obvious, and the best example of cellular dysfunction is that of primary anemia due to the absence of intrinsic gastric substance. Malnutrition, as conditioned by gastro-intestinal fistulae, presents itself as an interesting problem and one that is often difficult to explain adequately, although in most cases there is a short-circuiting process and a reduction in the amount of bowel, usually small intestine, through which the food passes. Occasionally one sees patients in whom there is very little change in the flow of the intestinal contents and yet who show marked alimentary malnutrition. Whether this is due to the diarrhea which frequently accompanies the lesion or to some intrinsic change in the gut is difficult to determine.

As a last consideration *chronic passive congestion* of cardiac origin affects the proper absorption of food from the intestinal tract. The elderly patient with cardiac disease often carries on rather well over a period of years and then begins to fail rapidly, with but little change in the cardiac function itself. Here we are probably seeing the cumulative effect of malnutrition over some length of time, suddenly manifesting itself in a general breakdown of the bodily mechanism.

UTILIZATION

A full diet having been presented to the organism and the end products of its digestion absorbed from the intestinal tract, we are led to a consideration of alimentary malnutrition dependent upon the improper utilization and storage of the nutrient substances by the body. Here, as in the previous considerations, we find that certain conditions will result in malnutrition in respect to all of the components of the diet, while others will affect one or more substances selectively. The former is true of anything that causes an increased demand generally, or more precisely when the total metabolism of the body is increased.

The chief cause of an increase in total metabolism is *physical activity*. By increasing energy expenditure it is quite possible to raise the caloric requirements by several thousand calories; if this is not met malnutrition will result. There is at present little evidence that this type of physiological demand carries with it an equal rise in the requirements for minerals and vitamins. However, one would suspect that those vitamins that have to do with cellular metabolism, either by affecting oxidation or reduction reactions or as enzymes, would necessarily be needed in larger quantities when the activity of the cells was increased. The expectation is perhaps justified that the working member of a group fed upon a minimally sufficient diet might develop a vitamin deficiency, while those not so occupied might escape. Certainly the appearance of pellagra in the children of the South can be explained upon the increased demand for the vitamin B complex incident to growth.

A second cause for increased total metabolism is *fever*. Here, of course, there are many contributing factors, such as anorexia and decreased intestinal activity, which make it difficult to differentiate clearly between them and total caloric increase due to fever. Malnutrition, however, because of the increased metabolism of fever, is common and the recognition of this fact has resulted in an understanding of the need of highly nutritive diets in any prolonged fever. The treatment of typhoid fever in recent years by high caloric diets has been effective in reducing the mortality from that disease and also

the extreme emaciation that used to result in those who survived.

Pregnancy is a third factor in the production of increased total metabolism. The basal metabolic rate alone is elevated on an average of 20 per cent, so that the pregnant woman, even at rest, will require that additional caloric intake. It is notable that nature reduces the maternal stores of vital elements, minerals and vitamins, so that the fetus may benefit. There is thus a consequent increased requirement for those substances, not only throughout gestation, but also during the period of nursing at the breast.

A fourth condition, of which mention has been made and wherein there is an increased rate of metabolism, is that of rapid *growth* occurring chiefly in infancy and at puberty.

Finally there are the various *dysfunctions of the endocrine system*. Hyperthyroidism is the chief example of this group, whether as the specific condition of Graves' disease or as a secondary manifestation of pituitary or ovarian dysfunction. Here, because of the increased rate of cellular activity, there is a marked rise in the total caloric requirement which, if not met, will result in malnutrition. Beyond this increase in metabolism there is also the specific effect of thyroxin upon the metabolism of the various elements of the diet, notably the vitamins A, B, and C and the minerals iron and calcium. The calcium effect is probably a secondary one mediated through the increased activity of the parathyroid glands, which react to the stimulation of the hyperactive thyroid just as do all the cells of the body. The mechanism of the vitamin reactions is not as yet clearly understood, but there is considerable evidence that some of the manifestations of hyperthyroidism are not essentially those of dysfunction but are rather those belonging to the vitamin deficiency diseases, conditioned by the increased demand for, and the poor utilization of, those substances in the presence of excess thyroid hormone.

A mechanism somewhat similar to those described above, in that there is an increased demand resulting from it, is that which develops from an increased rate of excretion of substances from the body. Diarrhea will accomplish this and may also have attendant changes in the intestinal tract which

affect the proper absorption of nutrient material. Urinary losses do not as a rule cause an increase in the general metabolic demands of the body, so that one does not see malnutrition of a general nature develop in patients with diuresis. There are, however, evidences of specific malnutritions in diabetes insipidus. Clinical scurvy and pellagra have been described in patients suffering from that disease, the apparent mechanism being the increased excretion of vitamin C and the vitamin B complex through the renal system.

Impaired Utilization.—Impaired utilization within the body of substances supplied in the diet may occur from a variety of conditions, again affecting one or all of the materials in different circumstances.

Toxemia from any cause which impairs cellular activity will be marked by improper use of the nutrient materials and the evidences of malnutrition may ensue. Thus the young adult not infrequently gains fifteen or more pounds in weight following the removal of diseased tonsils. One must certainly consider the previous state as being one of malnutrition due to the improper utilization of food because of cellular toxemia.

A second cause of toxemia resulting in impaired cellular function is that of the various metallic poisons. The principal example of this is lead neuritis, where the metal apparently disturbs the nervous tissue utilization of vitamin B from which there develops peripheral nerve degeneration and the familiar picture of neuritis, with wrist drop and pain. Liver and renal disease constitute the third toxic group, and are in many respects the most important. The retention of toxic substances of protein metabolism in renal disease and the loss of the detoxifying power of the liver in respect to the same group in hepatic disease are chiefly responsible for the cellular toxemia.

Endocrine diseases produce malnutrition. The chief example is a decreased metabolism conditioned by thyroid insufficiency. The myxedematous state is marked by apparent obesity but, as has been stated previously, this does not constitute the well nourished individual, and there is an accumulation of excess fat because of the improper metabolism, not only of the fats in the diet, but also of the carbohydrates. Similarly the myxedematous material is an abnormal metabolic

product of the proteins, so that their utilization by the body cells is likewise disturbed in the absence of a sufficient quantity of thyroxin.

It is interesting to note while considering this phase of nutrition that there apparently is a reduction in the amount of vitamin substances needed by the body in the presence of decreased thyroid activity, except for vitamin A. Since thyroxin is required for the proper transformation of the provitamin, carotene, into vitamin A in the liver, larger quantities of the latter substance are required when the thyroxin level is lowered. The other vitamins, however, seem to be subject to the reduced oxidation rate and hence are not required in as high a concentration as normally. Of the minerals, iron would appear to be the one whose utilization is primarily affected by the hypothyroid state. It is true that iron alone will not relieve the anemia that accompanies this condition, and it is only when thyroid substance is given that the anemia will be improved.

Finally, as another example of endocrine dysfunction resulting in malnutrition from improper metabolism, we may suggest diabetes mellitus. This affects primarily the utilization of carbohydrate and fats, but it may secondarily cause changes in the nutrition from many different abnormalities in cellular function as well as from the loss of material because of diuresis.

STORAGE

Brief reference should be made to the malnutritional state that results from the loss of the ability of the body to store the products of alimentation. Normally, there is a considerable reserve in the body of proteins, fats, minerals, vitamin A and the primary anemia factor of Castle. There is an adequate storage of carbohydrate as glycogen, and the ability of the body to convert fats and proteins into carbohydrates makes a considerable reserve supply. There is, however, a poor reserve of vitamins B, C, K, and D. The evidences of a deficiency of these substances will therefore appear rather rapidly if for any reason the diet is limited in respect to them, or if any of the factors mentioned above become active. Liver disease is particularly effective in bringing about malnutrition because of the disturbed metabolism and storage of many of

these substances. Keratomalacia may occur because of the lack of conversion of carotene into vitamin A and its storage; excessive bleeding may occur because of the failure to utilize vitamin K and the formation of prothrombin; and often a macrocytic anemia occurs in the absence of storage of the primary anemia factor.

Finally, let me quote from Burnet and Aykroyd⁶ a reminder that malnutrition is a problem not only for the physician, but also for all who are interested in improving the health of the population as a whole: "nutrition is an economic, agricultural, industrial and commercial problem as well as a problem in physiology."

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HYPERINSULINISM: WITH A REPORT OF TWO CASES OF
ADENOMA OF THE ISLETS OF LANGERHANS

A RELATIVE or absolute excess of endogenous insulin, hyperinsulinism, may cause a chronic hypoglycemia. The symptom complex which results is due to functionally overactive islet cells, a hyperplasia of the islet cells, or to tumors, benign or malignant, of the islets of Langerhans. The present conception of hyperinsulinism is based on a series of observations dating from the discovery of the islet tissue in the pancreas by Langerhans in 1869. The observations made by Banting¹ and his co-workers on the effects of large doses of insulin (1921) were especially important. Recognition of signs and symptoms identical with those of insulin reactions, but in patients who had not received insulin, prompted Harris (1923)² to postulate a new clinical entity "hyperinsulinism."

Low values for blood sugar were noted and the abnormally great tolerance which patients suffering from this disease had for carbohydrate was recognized. Wilder (1927)³ and his co-workers removed all doubt as to the genuineness of hyperinsulinism when they recovered large amounts of insulin from an islet cell carcinoma and from the metastatic growths in the liver. Howland⁴ (1929) reported the first cure of a case of hyperinsulinism following the removal of an adenoma of the islets of Langerhans. Whipple⁵ collected fifty-six cases of tumors of the islets of Langerhans reported prior to 1938; forty-three were adenomata and thirteen were malignant. It is of interest that Whipple's⁵ first six patients with this disease were referred to him from the Neurological Institute.

The subject of hyperinsulinism has been adequately reviewed by Wilder,⁷ Sigwald,⁸ Wauchope,⁹ Whipple and Frantz,⁶

Harris,¹⁰ Womack,¹¹ and Whipple.⁵ The newness of the disease as a recognized clinical entity, the individual differences and the opportunities for investigation, which may throw some light on the mechanism of insulin action, justify the reporting of every new case when circumstances permit adequate observations. It is for these reasons that the clinical aspects of the following cases recently observed are presented in some detail:

ILLUSTRATIVE CASES

Case I.—A white girl, aged nineteen years, weighing 108 pounds (49 Kg.) and measuring 62 inches (155 cm.), was admitted to the Pennsylvania Hospital on March 27, 1938, complaining of attacks of vertigo, headaches and unconsciousness. These attacks began in March, 1937, with sudden loss of consciousness one afternoon although subsequent attacks occurred for the most part in the morning before breakfast. The patient was found on the floor approximately two hours after the onset of the attack. She was roused with difficulty but was able to resume her duties. In September (1937) she had spells of weakness on rising in the morning and a feeling that she was going to faint. She had an incomplete abortion in October, 1937.

One morning in November (1937) she felt weak and dizzy. She dressed, went downstairs, and while preparing breakfast became emotionally upset and shortly lost consciousness. She was seen by Dr. W. B. Turner, who admitted her to the Carlisle Hospital. A blood sugar level of 23 mg. per 100 cc. was found. After two days of intermittent intravenous dextrose therapy she recovered. A high carbohydrate diet was prescribed, but the blood sugar values remained low, between 35 and 45 mg. per 100 cc. She was discharged from the hospital after one week. Two weeks later she was readmitted in a stuporous condition but responded readily to intravenous dextrose. The blood sugar level varied from 30 to 50 mg. per 100 cc. There were no convulsive seizures.

A dextrose tolerance test at that time revealed the following values for blood sugar: fasting, 28 mg.; one-half hour, 90; one hour, 97; and at two hours, 100 mg. per 100 cc. A postprandial blood sugar value was found to be 57 mg. per 100 cc. The sedimentation rate was 12 mm. in one hour and the basal metabolic rate was plus 5 per cent on two occasions. The blood coagulation time and the bleeding time were normal. The blood pressure was 110 mm. of Hg systolic and 80 mm. diastolic.

The patient continued to suffer from weakness and vertigo in periods of two or three consecutive days at three- to five-week intervals. The attacks were more severe during menstruation, though during some menses there seemed to be no increase in the susceptibility to attacks. She had had no attacks for three weeks prior to her admission to the Pennsylvania Hospital.

Examination on admission (March 27, 1938) revealed: considerable flushing about the neck and at times of the face, hair and skin oily, some acne, complete edentia, some reddening of the anterior tonsillar pillars and diseased tonsils. There was an unusually great separation of the nails from the matrix of fingers and toes, and there was moderate proximodistal tilting of the nails. The hands and feet were moist. There was a slight tendency to masculine distribution of suprapubic hair and there was a considerable growth of hair on the extremities.

Laboratory data. The fasting level of the blood sugar (March 28) was 58 mg. per 100 cc. and the results of a six-hour dextrose tolerance test (100 Gm. dextrose) on March 30 were as follows: fasting blood sugar level, 66 mg.; one-half hour, 106; one hour, 107; two hours, 100; three hours, 123; four hours, 93; five hours, 88; and six hours, 62 mg. per 100 cc.

The blood count and the urine were normal. The blood urea nitrogen level and the urea clearance were normal as was also the levulose tolerance test for liver function. An analysis of the fractional gastric contents showed a low free and total acid. The stools were normal.

Roentgenograms of the skull, particularly of the sella turcica and of the heart, lungs and gastro-intestinal tract, were not remarkable. The electrocardiogram was normal.

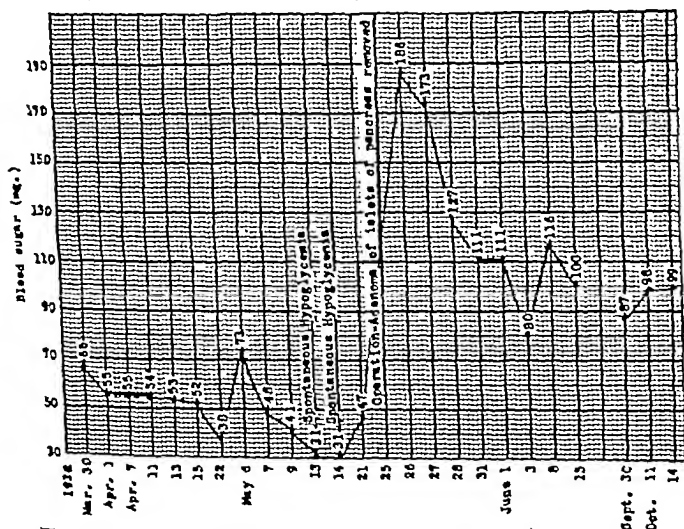


Fig. 87.—The hypoglycemic values before, the transitory hyperglycemia immediately following, and the normal blood sugar levels from three days to four months after, the removal of an adenoma of the islets of Langerhans are presented (Case I).

Diet. Throughout the following studies a weighed diet containing 65 Gm. of protein, 200 Gm. of carbohydrate, and 93 Gm. of fat (2400) calories divided into three meals and three nourishments was allowed.

The preoperative blood sugar values (fasting) were all below normal (70 mg. per 100 cc.) and during spontaneous attacks of unconsciousness they were as low as 28 mg. (Fig. 87).

The patient appeared well and for several weeks it seemed that the inactivity of ward life was sufficient to counteract the tendency to spontaneous attacks of hypoglycemia. Moderate exercise did not precipitate an attack.

Attempts were made to determine the ease or difficulty with which attacks might be provoked and also to learn if the susceptibility to attacks altered from time to time. The following studies made this clear.

Provocative tests. Omission of breakfast, while the gastric contents were

being extracted for examination (April 5), was followed at 11 A.M. by vertigo and headache, and the patient complained of feeling cold. Prompt relief was secured by giving orange juice. Though low values for blood sugar were obtained no spontaneous attacks (usually considered characteristic of hypoglycemic reactions) occurred during a *twenty-four-hour fast*.

The *effect of exercise* was next tried. On April 8 the usual breakfast was given at 8:15 A.M. and the patient spent three twenty-minute periods exercising on a rowing machine between 9:30 and 11:30 A.M. At 11:30 she complained of hunger and of slight headache but was well otherwise. The blood sugar values were: 8 A.M. (fasting), 52 mg.; 10 A.M., 57; 12 noon, 51; and 2 P.M., 50 mg. per 100 cc. The patient was not allowed any breakfast (no

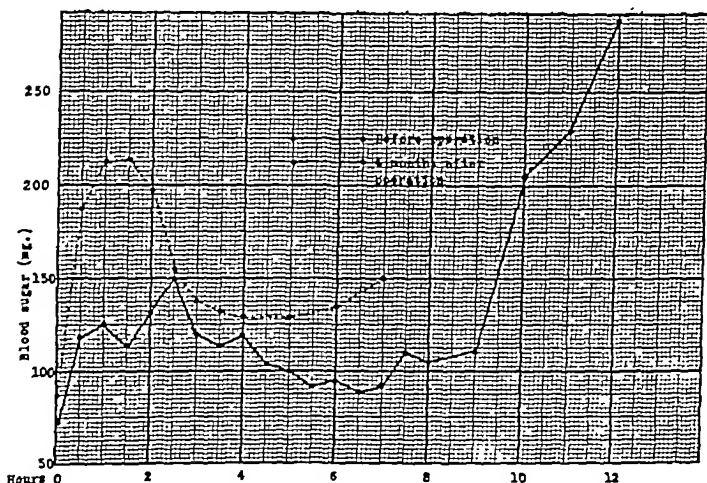


Fig. 88.—The abnormally great ability to remove dextrose from the blood in spite of increases in the rate of dextrose administration by venoclysis, from 28 Gm. per hour at the end of five hours, to 36 Gm. per hour at seven hours, to 44 Gm. per hour and at nine hours to 54 Gm. per hour before operation, is contrasted with the normal blood sugar level response when dextrose in a 15 per cent solution was given continuously at the rate of 28 Gm. of dextrose per hour after operation (Case I).

food after 8 o'clock the previous evening) and the exercise test was repeated on April 11. The blood sugar value at 8 A.M. was 54 mg. per 100 cc. and 31 mg. at 10 A.M., when there was muscle twitching and the patient was pale but did not perspire. She felt tired and when returned to bed promptly slept, but she could be aroused easily. She had fully recovered by 11:15 A.M. In spite of continued exercise and without food the blood sugar had increased to 40 mg. per 100 cc. at 12 noon and to 46 mg. at 2 P.M. This increase, though slight, was attributed to spontaneous epinephrine response to the low blood sugar level.

In an attempt to determine the approximate rate of withdrawal of sugar from the blood before operation a *continuous intravenous administration of dextrose* was begun on May 6 at 7 A.M. Blood sugar values were obtained

at one-half hour intervals. Twenty-eight Gm. of dextrose (in 15 per cent solution) in distilled water were given each hour, from 7 A.M. until noon (five hours). An early increase in the blood sugar concentration was soon overcome (Fig. 88) and it appeared obvious that this rate of dextrose administration would not cause a hyperglycemia. The rate was increased to 35 Gm. per hour, and after seven hours to 44 Gm. and at nine hours to 52 Gm. per hour. No increase in blood sugar values was found until 5:00 P.M. (after ten hours of continuous dextrose administration). A rapid elevation of the blood sugar ensued; 203 mg. per 100 cc. after ten hours (5 P.M.), 230 mg. at eleven hours, and 286 mg. at twelve hours. Glycosuria increased from 1.3 per cent at 4 P.M. to 10 per cent at 6:30 P.M. and was 9.9 per cent at 8:10 P.M.

The patient felt unusually well during the test. The total dextrose given in twelve hours was 3700 cc. of a 15 per cent solution, or 555 Gm. The amount lost in the urine was 182 Gm. and the amount retained 373 Gm.

The daily total sodium chloride excretion in the urine varied from 2 to 5 Gm. in twenty-four hours and an increase to 8.6 Gm. occurred on one day when the intake was increased by 15 Gm. The plasma chloride was 612 mg. per 100 cc.

On May 13, the patient began to *menstruate*. At 8 A.M. (May 13) she had a spontaneous attack of clinical hypoglycemia just before breakfast. Rapidly deepening unconsciousness followed. By 8:25 A.M. she was very pale, with pupils widely dilated, and there were frequent muscle twitchings of the limbs and body. Her blood pressure was 110 mm. systolic and 74 mm. diastolic and the blood sugar level was 31 mg. per 100 cc. Epinephrine, 1 cc. (1:1000 solution) was given subcutaneously (no dextrose or other nourishment) at 8:25 A.M. and by 8:35 consciousness was restored and at 9 A.M. she complained of being nervous and was emotionally unstable but conscious and cooperative. Her blood pressure was 154 mm. systolic and 74 mm. diastolic.

Another spontaneous attack occurred on May 14 at 3:45 A.M. The patient's face was flushed and she tossed about in her bed and could not be aroused. The blood sugar level at 3:52 was 31 mg. per 100 cc. Epinephrine was given at this time and was repeated at 3:58. Within five minutes of the second dose the restlessness subsided and she could be aroused and was cooperative. She was given 6 ounces of orange juice.

Spontaneous attacks occurred on May 15 and May 22. On each occasion orange juice was given and consciousness was quickly regained.

The acute onset, the chronic course, the hypoglycemia with symptoms especially prominent at the time of the menstrual period and at the end of the longest period in the day without food, the relief of symptoms by taking food and on receiving epinephrine, the characteristic dextrose tolerance curve and the remarkable rapidity with which dextrose was removed from the blood stream, all favored the diagnosis of hyperinsulinism.

The severity of the disorder and the rhythm with which great susceptibility to spontaneous attacks occurred with intervening periods during which, unlike cases of functional hyperinsulinism, it was difficult to precipitate an attack, led to a preoperative diagnosis of adenoma of the islets of Langerhans.

Operation: For twenty-four hours prior to operation liberal amounts of carbohydrate were given by mouth. The fasting blood sugar value on the day of operation (May 25) was 63 mg. At 11 A.M., 500 cc. of a 10 per cent solution of dextrose was given in normal saline by venoclysis.

At 11 A.M. the patient was given morphine sulfate, gr. $\frac{1}{6}$, and atropine sulfate, gr. $\frac{1}{150}$. One hour and forty-five minutes later spinal anesthesia was induced, using 200 mg. of primocaine. A transverse incision was made 4 cm. above the umbilicus, dividing both rectus muscles. The lesser peritoneal cavity was entered through the gastrocolic omentum and the pancreas was exposed. No tumor was visible, but a round hard mass, approximately 1.5 cm. in diameter, was palpated in the tail of the pancreas near the distal end. Careful palpation of the pancreas elsewhere failed to reveal any other area suggestive of tumor. The indurated mass of tissue was excised. Several small vessels were ligated with fine silk and the defect in the pancreas was closed with interrupted fine silk sutures. The gallbladder and liver appeared normal. The abdominal incision was closed anatomically, using interrupted sutures of silk in all the layers. The peritoneal cavity was not drained.

Following operation there was a slight febrile reaction, the patient's temperature reaching a peak of 101° F. on the third postoperative day and gradually receding, to reach normal on the thirteenth postoperative day. During this period the patient at times complained of pain in the left flank and was slightly tender below the twelfth rib on the left side. Convalescence otherwise was undisturbed.

Subsequent Course.—Four hours after operation the blood sugar level was 186 mg. per 100 cc. The following morning it was 173 mg. and subsequent values were normal. There was a practically normal response to the dextrose tolerance test three days after operation, in contrast to the low curve obtained preoperatively (Table 1).

TABLE 1

DEXTROSE TOLERANCE TESTS (6 HOUR)

The low type of curve obtained in response to 100 Gm. of dextrose before operation is contrasted with normal responses two weeks and four months after the removal of the adenoma of the islets of Langerhans (Case I).

	Fasting.	$\frac{1}{2}$ hr.	1 hr.	2 hrs.	3 hrs.	4 hrs.	5 hrs.	6 hrs.
Blood sugar (mg. per 100 cc.).	Preoperative test (April 1, 1938)							
	66	106	107	100	123	93	88	62
	Postoperative test (June 8, 1938)							
	116	154	173	139	94	92	102	102
	Postoperative test (October 11, 1938)							
	87	117	171	90	102	114	97	97

A prompt hyperglycemic response followed the continuous administration of dextrose on the second day after operation. The dextrose was given at the same rate as on the previous similar test.

The patient was re-admitted on September 17, 1938, in order that comparative metabolic studies might be made. She had enjoyed excellent health in the interim. There were no changes observed on physical examination with the exception that she had gained 7 pounds (3.1 Kg.).



METRIC SYSTEM

3

Fig. 89.—Photograph of the incised adenoma (Case I).



Fig. 90.—A section of the adenoma reveals a fibrocellular structure with thin cords and rosette cell arrangements, hyaline fibrous tissue and degenerative changes. No mitotic figures were seen (Case I).

The patient's diet was unlimited in the interim but, on re-admission, for the sake of uniformity, the diet employed on her previous admission (65 Gm. of protein, 200 Gm. of carbohydrate and sufficient fat to make a total of 2400 calories) was resumed.

After ten days the various tests done before operation were repeated.

The dextrose tolerance test was normal (Table 1). A normal response to intravenous dextrose was obtained (Fig. 88). The low total sodium chloride excretion in the urine and the poor response to added sodium chloride in the diet before operation were in contrast to the normal excretion and a good response to added sodium chloride four months after operation (Table 2).

TABLE 2

SODIUM CHLORIDE OUTPUT IN URINE

The low sodium chloride excretion before, is contrasted with the normal values obtained after, operation (Case I).

Preoperative.			Postoperative.		
Date, 1938.	Volume of urine (cc.) per diem.	Urine chlorides, Gm. per diem.	Date, 1938.	Volume of urine (cc.) per diem.	Urine chlorides, Gm. per diem.
June 6	865	2 0	Sept. 21	1500	6.9
14	1380	4.6	22	1550	6.8
17	1240	3.3	23	1510	9.6
18	1175	3.7	24	1100	7.3
19	1090	3.1	25	1640	7.6
20	2010	5.0	26	1370	8.5
22	(15 Gm. NaCl added to intake)		27	1460	7.8
	1420	8.6	28	1600	7.3
24	1620	4 1	29	1480	4.1
			30	1580	9.8
			Oct. 1	(15 Gm. NaCl added to intake)	
				1320	14.7

Fasting plus exercise produced marked hypoglycemic values when fasting alone failed to produce symptoms before operation. The observations repeated four months after the operation revealed but a slight reduction in the blood sugar level (Table 3).

TABLE 3

EFFECT OF FASTING PLUS EXERCISE ON THE BLOOD SUGAR VALUES (MG. PER 100 CC.)

The effect of fasting and exercise on the blood sugar before, is compared with that obtained four months after operation (Case I).

Time.	8 A.M.	10 A.M.	12 N.	2 P.M.
Preoperative blood sugar.	54	31	40	46
Postoperative blood sugar	99	92	85	92

Periods of exercise (twenty minutes each) were begun at 8 A.M. and repeated at hourly intervals.

Case II.—A white youth, aged eighteen years, weighing 133 pounds (60 Kg.) and measuring 68 inches (160 cm.), was admitted to Dr. Hobart Reimann's Service at the Jefferson Hospital on June 22, 1939. He complained

of having had about twelve attacks of unconsciousness associated with convulsions. The first attack occurred in November, 1936. A hypoglycemia had been found by his attending physician in 1937.

The patient's physical condition was good, though he had lost 13 pounds (6 Kg.) in the two months preceding admission.

He had several spontaneous attacks of unconsciousness with convulsions while in the hospital. These were promptly relieved by epinephrine alone and by dextrose given intravenously. The blood sugar levels were 19 mg., 23 mg., 18 mg., and 26 mg. per 100 cc. during attacks and there was a continuous hypoglycemia, the blood sugar values (fasting) varying from 31 to 42 mg. per 100 cc.

A six-hour dextrose tolerance test (100 Gm. dextrose) revealed capillary and venous blood sugar and phosphorus values as follows:

	Capillary blood sugar, mg. per 100 cc.	Venous blood sugar, mg. per 100 cc.	Blood phosphorus, mg. per 100 cc.
Fasting	42	39	2.5
1 hour	99	81	1.78
2 hour	108	79	1.10
3 hour	93	86	2.10
4 hour	40	36	1.4
5 hour	36	35	1.5
6 hour	35	34	1.4

The blood cholesterol was 118 mg. per 100 cc. (free cholesterol 38 mg. and cholesterol esters 80 mg.).

The blood count, basal metabolic rate, ophthalmoscopic and neurologic examinations, roentgen examination of the sella turcica, cholecystogram, electrocardiogram, and liver function studies were negative. The sodium chloride excretion was low (7.7 Gm. in 2200 cc. of urine), but was within the normal range.

The chronic hypoglycemia, the attacks of unconsciousness and convulsions which were promptly relieved by dextrose therapy, the long periods without symptoms, and the phases during which the attacks were spontaneous warranted a preoperative diagnosis of a tumor of the islets of Langerhans.

An adenoma, the size of a small English walnut, was removed from the tail of the pancreas by Dr. G. P. Muller on July 12, 1939.

Immediately after operation, the patient having had no dextrose therapy, the blood sugar was 87 mg. per 100 cc. Subsequent values were normal, with the exception of a level of 166 mg. found on the evening of July 12. A dextrose tolerance test on July 24 revealed: Fasting, 82 mg. of sugar per 100 cc.; one hour, 120 mg.; two hours, 86 mg.; three hours, 76 mg.; four hours, 91 mg.; five hours, 90 mg.; and six hours, 89 mg. per 100 cc. The postoperative convalescence was complicated by a mild but continuous fever for eight days. The patient had considerable abdominal pain which was troublesome for three weeks after the operation.

The tumor was encapsulated, but histologic examination revealed active hyperplasia of the epithelial cells, mitosis and the presence of acini and islet cells. The diagnosis was: Adenoma of the islets of Langerhans which was probably undergoing malignant changes.

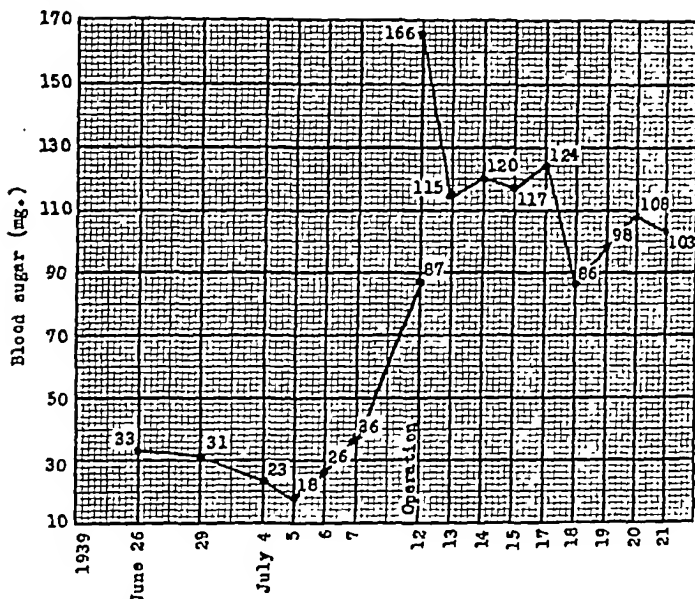


Fig. 91.—The chronic hypoglycemia before, and the transitory hyperglycemia following promptly after removal of the tumor of the islets are illustrated. The return of the blood sugar level to the normal zone is also shown (Case II).

DISCUSSION

A chronic hypoglycemia may occur when the mechanism which regulates the blood sugar level is disturbed. To be considered are diseases of: (1) the pancreas, as (a) functional hypertrophy of the islets of Langerhans, or (b) tumors, benign or malignant, of the islets; (2) the liver, (a) extensive liver disease such as acute yellow atrophy, and (b) chronic infectious hepatitis; (3) the adrenals, Addison's disease; (4) the hypophysis, (a) Simmonds' disease, (b) tumor (pituitary or in hypothalamus) depressing the activity of the anterior lobe. Mild degrees of hypoglycemia may be associated with (5) disease of the thyroid gland, hypothyroidism, and (6) disturbances of the sympathetic nervous system.

Disease of the Pancreas.—1. *Functional Hyperinsulinism.* This is believed to be due to the liberation of abnormally large amounts of insulin by overactive islet cells. This may be a relative hyperactivity closely associated with an impaired glycogenolytic function of the liver or to poor glycogen storage.

Nevertheless, there are a considerable number of patients who have mild degrees of hypoglycemia without demonstrable liver disturbances and who have not tumors of the islets of Langerhans. These patients complain of fatigue, nervousness, headaches, disorientation, vertigo, inability to concentrate, epigastric pain and extreme hunger. These symptoms are particularly noticeable when meals are delayed, and especially after active physical exercise. Very low values for blood sugar are not common and complete relief from symptoms follows the taking of food. Loss of consciousness rarely if ever occurs in the adult. Dextrose tolerance tests, when carried over six hours, usually reveal a low curve, but of greater diagnostic value are the blood sugar values below 60 mg. per 100 cc. at five and at six hours after the administration of the dextrose.

A true and serious form of functional hyperinsulinism occurs in infants born of mothers who have uncontrolled diabetes. Unless anticipated and prevented these attacks may prove fatal. Hartman and Jaudon¹² have reviewed this subject, and they attach importance to the hypoglycemia occurring in infants of diabetic mothers. Duncan and Fetter¹³ regard an otherwise unexplained gain in the diabetic mother's tolerance for carbohydrates in the last trimester of pregnancy as unfavorable for the child as it is due in all probability to an abnormally active fetal pancreas.

2. Tumors of the Islets of Langerhans.—These may be (1) benign adenomas, or (2) carcinomas, with or without metastasis. It may be impossible to distinguish between the two clinically. The benign adenomas usually cause less severe clinical manifestations and the tendency to progressiveness may not be so marked as when the tumor is malignant. We believe it is significant that patients with adenomas of the islets have distinct phases of extreme sensitiveness to exercise, fasting, menstruation, diarrhea and loss of weight, which tend to precipitate hypoglycemic reactions with longer intervals between in which it is difficult to provoke an attack of hypoglycemia. Furthermore, the cycles of increased sensitiveness are most pronounced during some, but not during all, menstrual periods. Some patients with adenomas, when subjected to a dextrose tolerance test, have an early hyperglycemia. This was not the case in either of our patients. The malignant tumors are more

apt to cause more extreme degrees of hypoglycemia which are more difficult to correct. The attacks tend to be more frequent also and are precipitated with greater ease by merely withholding food. Malignant tumors occur in young as well as middle-aged patients of either sex. Federoff's patient, referred to by Whipple,⁶ was a male, sixteen years of age, and Judd¹⁴ reported a case of carcinoma of the islets of Langerhans in a girl aged eighteen years.

3. **Disease of the Liver.**—There is no difficulty in recognizing the cause of the hypoglycemia in patients who have acute yellow atrophy of the liver. These patients are gravely ill and have other signs of hepatic disease which are more obvious than the hypoglycemia. Rabinowitz¹⁵ has presented the salient clinical features as well as the hypoglycemic tendencies in these cases and Sprague¹⁶ has demonstrated that animals in which the liver has been damaged or partially extirpated have an increased sensitivity to insulin. Mann¹⁷ produced profound hypoglycemia in dogs by hepatectomy and tendencies to hypoglycemia by partial hepatectomy. Any disease causing extensive damage to the liver is likely to cause mild hypoglycemia, especially after fasting or attacks of diarrhea.

A greater diagnostic problem is presented by patients who are not acutely ill but who, on careful investigation, are found to have disease of the biliary tract. Every patient found to have a chronic hypoglycemia should be investigated for a possible *infectious hepatitis*. Conn¹⁸ and his associates have reported six cases of chronic hypoglycemia of hepatic origin. In one (Case I) attacks of unconsciousness occurred from nine to twelve hours after the evening meal and the blood sugar values, while the patient was fasting, ranged from 14 to 18 mg. per 100 cc. Symptoms which were typical of a severe hypoglycemia were promptly corrected by giving dextrose intravenously. Dextrose tolerance tests showed an impaired ability to remove absorbed dextrose from the blood stream in the normal length of time, yielding a curve, during the first two or three hours after the ingestion of this dextrose, similar to that obtained in mild diabetes and not like the one usually seen in hyperinsulinism due to a functional disturbance or to a tumor of the islets. The test, carried over four and one-half hours, revealed a return to hypoglycemic levels. This type of

curve in the presence of low fasting values for blood sugar strongly suggests hepatic injury.

Retention of the bromsulphalein dye, an abnormally low serum protein with a reversal of the albumin-globulin ratio, hyperbilirubinemia (2.5 mg. per 100 cc.), and an impaired galactose tolerance, gave further evidence of liver disease. A cholecystogram revealed slight visualization of the gallbladder.

A gallbladder containing a calculus and 2 or 3 ounces (60 to 90 cc.) of pus was removed. A biopsy of the liver revealed an active chronic cholangiolitis, biliary cirrhosis, cloudy swelling and fatty infiltration. After operation the level of the blood sugar became normal as the evidences of hepatic damage disappeared and there were no recurrences of the spontaneous attacks of hypoglycemia.

It is not our intention to discuss all of the causes of hypoglycemia. It should be stated, however, that disease of the adrenals, the hypophysis, the thyroid gland, and disturbances of the sympathetic nervous system should be considered as possible causes in cases of chronic hypoglycemia. Their clinical characteristics should preclude any difficulty in establishing the diagnosis.

TREATMENT OF CHRONIC HYPOGLYCEMIA

The treatment depends upon the cause of the hypoglycemia. The actual attack of hypoglycemia due to *functional hyperinsulinism* is readily corrected by the oral administration of a quickly absorbable carbohydrate such as dextrose, orange juice or syrups, or by the intravenous administration of 25 cc. of a 25 per cent solution of dextrose. The chief object in treating patients with this disorder is the prevention of attacks.

The carbohydrate foods which are quickly absorbed are to be avoided because of their insulogenic action and because of the increase in insulin sensitivity which follows their use. The carbohydrate content of the diet should not exceed 150 Gm. and is best provided in a form which is slowly absorbed, such as cereals, bread, fruits and vegetables. Fat in liberal quantities is allowed and the total diet should have a high caloric value. Undernutrition should be avoided. A loss in weight exaggerates symptoms in true cases of functional hyperin-

sulinism. Additional mid-morning, mid-afternoon and late evening nourishments are valuable in preventing symptoms. (A sample diet which has proved useful in the treatment of this disorder is presented in Table 4.) John¹⁰ has suggested

TABLE 4

DIET LIST FOR THE TREATMENT OF FUNCTIONAL HYPERINSULINISM

90 Gm. protein, 256 Gm. fat, 125 Gm. carbohydrate. 3164 calories—Six feedings.

Food.	Weight, Gm.	Household measure.	Protein.	Fat.	Carbohy- drate.	Menu.
Breakfast:						
Cereal.....	20	½ cup	3	16	Oatmeal, cream.
Bacon—fried crisp	15	2 slices	3	8	...	Bacon.
Cream (20%)....	120	½ cup	4	24	4	Coffee with cream.
Fruit 12%.....	100	1 serving	12	Orange juice.
Mid-morning:						
Egg nog
Egg.....	..	1	7	5	..	Egg nog.
Cream (20%)	120	½ cup	4	24	4	..
Sugar.....	5	1 tsp.	5	..
Crackers.....	6	2	1	1	4	Crackers, buttered.
Butter.....	10	2 tsp.	..	8.5
Lunch:						
Meat.....	60	2 oz.	14	10	..	Cold beef.
3% vegetable (salad).....	100	1 sauce dish	2	3	Tomato and let- tuce salad with mayonnaise.
9% vegetable....	100	1 sauce dish	3	..	9	Peas with cream.
Bread.....	30	1 slice	3	..	16	Bread and butter.
Cream (20%)....	60	½ cup	2	12	2	Coffee with cream.
Butter and may- onnaise.....	45	3 tbsp.	..	38
Mid-afternoon:						
Crackers.....	6	2	1	1	4	Crackers, buttered.
Cheese, Am.....	15	½ oz.	4.5	5.5	..	Cheese.
Butter.....	30	2 tbsp.	25
Dinner:						
Meat.....	120	4 oz.	28	20	...	Broiled lamb chops.
Potato.....	100	1 small	2	...	18	Potato with cream.
9% vegetable....	100	1 sauce dish	3	9	Buttered beets.
Cream.....	60	½ cup	2	12	2	Tea.
Butter.....	45	3 tbsp.	..	38
Between Dinner and Bedtime:						
Cream (20%) .	120	½ cup	4	24	4	Peach with cream.
Fruit 12%.....	100	1 serving	12	..
Total.	90.5	256	124	..

A sample diet restricted in carbohydrate content with a high fat allowance and liberal calories for patients with hyperinsulinism.

giving small doses of insulin before meals to prevent the post-prandial increase in the blood sugar which has an insulogenic effect. It is well to remember that these patients, especially those who are thin, are extremely sensitive to insulin. This sensitiveness is doubtless increased by the great amounts of

carbohydrate which these patients are usually given. Physical activity should be minimal.

Surgical treatment has no place in the treatment of functional hyperinsulinism.

Tumors of the Pancreas.—If a diagnosis of tumor of the pancreas is made by exclusion of the extrapancreatic causes of hyperinsulinism, surgical intervention is indicated.

The pancreas is exposed (as in Case I) and is carefully palpated. Most adenomas occur in the tail and are easily identified. When no tumor is found in the tail or body of the pancreas, Whipple⁶ advises mobilizing the duodenum to the midline by incising the peritoneum along the curve of the duodenum, thus obtaining exposure of the posterior surface of the pancreas and allowing free examination of the head of the pancreas. A tumor in the head is apt to be overlooked unless carefully sought for.

A dramatic cure of the chronic hypoglycemia follows the removal of the responsible tumor. Failing such a result a second tumor should be looked for.

Surgical removal is the only treatment for tumors of the islets of Langerhans.

Infectious Hepatitis.—Chronic hypoglycemia due to an ascending infectious hepatitis is easily identified if the condition is kept in mind. Eradication of the infection is the object of treatment. This may be done by removing or draining an infected gallbladder, if present. Biliary drainage is worth a trial.

It is not our purpose to discuss the treatment of the other causes of chronic hypoglycemia, notably necrosis of the liver and disease of the hypophysis, thyroid and adrenal glands.

SUMMARY AND CONCLUSIONS

1. The two patients suffering from hyperinsulinism due to adenomas of the islets of Langerhans were cured when the tumors were removed.
2. There was in each case an unusually great tolerance for carbohydrate before, and a normal tolerance for carbohydrate after, the operation.
3. The combination of exercise and fasting was the most effective means of provoking the symptoms of hypoglycemia.

4. There were evidences of spontaneous correction of the symptoms of hypoglycemia and there was a prompt response to epinephrine injected subcutaneously.

5. The chloride excretion was low before, and normal after, operation (Case I).

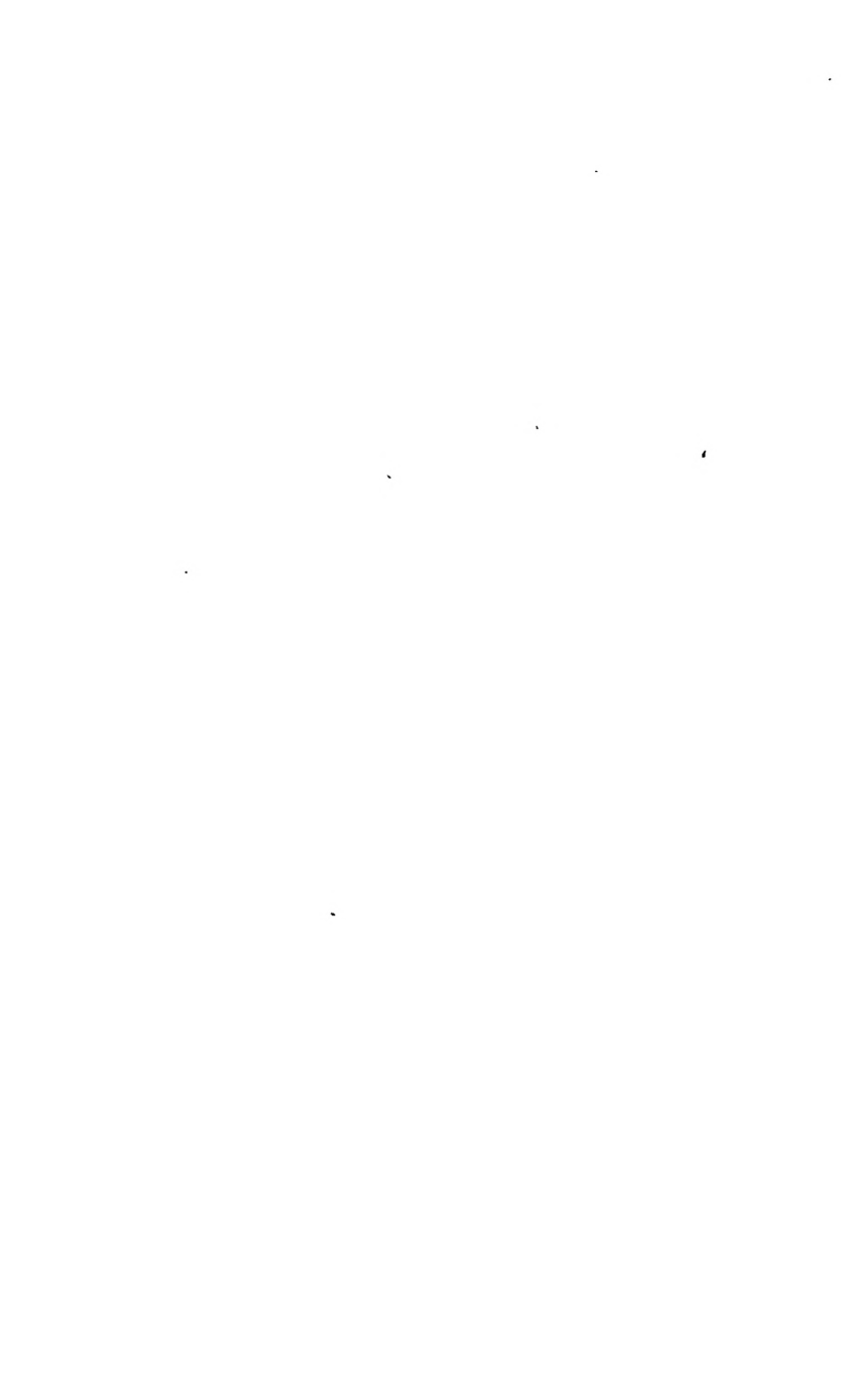
6. The fasting blood sugar level was invariably below normal in both cases before operation. A transient hyperglycemia followed promptly upon removal of each adenoma and normal fasting blood sugar values were restored within three days in one case and twenty-four hours in the other. Abdominal discomfort with a mild degree of fever followed operation for thirteen days in one and eight days in the other case.

7. The treatment of hyperinsulinism is *surgical* when this condition is due to a tumor of the islets of Langerhans. The treatment is *medical* when the condition is a functional overactivity of otherwise normal islets of Langerhans.

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CLINIC OF DRS. JOHN K. DURKIN AND FERDINAND FETTER

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DIFFERENCES IN THE TREATMENT OF THE FAT AND THE THIN DIABETIC PATIENT

It is generally agreed that the object of treatment of the patient with diabetes mellitus is the restoration of normal metabolism. Obviously, this means the maintenance of a normal blood sugar and freedom from glycosuria. In addition, however, the restoration of normal metabolism should mean establishing and maintaining a body weight at, or a trifle below, the standard for the patient's age, sex, and height. In our experience, this latter aspect of the treatment of the diabetic patient is frequently neglected, particularly in regard to weight reduction in obese patients. Accordingly we wish to emphasize the importance of establishing a normal weight in treating the diabetic patient.

If a satisfactory weight is to be attained, the thin diabetic needs a diet containing 30 to 35 calories or more per kilogram of ideal weight, and the fat diabetic should receive a diet of 15 to 20 calories per kilogram. In addition to the obvious differences in the diet in the two groups, there is a marked difference in the need for insulin in the overweight and the underweight diabetic. In general, it is our experience that the uncomplicated obese adult diabetic patient almost never needs insulin if his weight is reduced. The thin diabetic, however, practically always needs insulin.

TREATMENT OF THE OBESE DIABETIC PATIENT

As Duncan¹ has pointed out, diabetes is mild in any patient if he has never taken insulin and is considerably overweight, regardless of the initial blood sugar level. With weight reduction and the corresponding reduction of the total metabolism, the apparent need for insulin disappears. We therefore do not give insulin to overweight adult patients with uncomplicated

diabetes. We find that if the patient loses weight by adhering to a low-caloric diet (containing 15 to 20 calories per kilogram of ideal weight), the blood sugar falls to normal without the use of insulin. The weight loss should not be too rapid; two to three pounds a week is enough.

In this connection, the recent paper by Newburgh and Conn² is of interest: These workers agree with us that weight reduction in obese patients with hyperglycemia results in a fall of the blood sugar to normal levels. However, they regard the obesity as the chief abnormality, with the hyperglycemia as a secondary factor, and believe that after weight reduction these patients need not be considered as having diabetes. While this is an interesting conception, we think it is wiser to regard these patients as potential diabetics who still need careful following. If they are led to believe that their diabetes is "cured," they are apt to allow dangerous pounds to accumulate, or neglect infections or other complications when they develop.

The diets that we have been prescribing for obese diabetic patients contain sufficient protein to maintain protein metabolism (about 1 Gm. of protein per Kg. of ideal weight), 90 to 120 Gm. of carbohydrate, and enough fat to make up the desired number of calories (usually about 1200 per day). These diets are comparatively low in fat, averaging 50 to 55 Gm. per day. This restriction of the large calorie-container, fat, as well as restriction of carbohydrate, is particularly important, and we wish to emphasize the value of this restriction in reducing the blood sugar level. Incidentally, we want to point out the difference between spontaneous loss of weight in the untreated diabetic, which results from lack of control of the disease, and deliberate loss of weight in the overweight diabetic as a part of the process of control and treatment of the diabetes. The latter is desirable, while the former is not.

If the obese diabetic patient co-operates and follows the prescribed low-caloric diet, his diabetes is promptly controlled as his weight falls. If he refuses to follow the low-caloric diet and maintains his weight, the blood sugar level stays high. If insulin is then given in an effort to control the diabetes, we find that large doses are needed, and that even then the control is not complete.

We shall now present illustrative cases, showing the methods and results of treatment in various obese diabetic patients. The records presented are typical of a number of similar patients treated in the diabetic out-patient clinic.

Case I.—This case will show: (1) an increase in severity of the diabetes with a gain in weight, and (2) control of the diabetes with a reduction in weight.

On September 20, 1937, a dextrose tolerance test was done on this patient with the following results: fasting blood sugar, 105 mg. per 100 cc.; one hour after 100 Gm. of glucose, 141 mg. per 100 cc.; two hours after, 103 mg. per 100 cc.; and three hours, 99 mg. per 100 cc. This, of course, is not a diabetic curve. At that time the patient weighed 145½ pounds (17 per cent overweight).

When she was next seen, on January 27, 1939, she had gained weight to 163¾ pounds (25 per cent overweight) and her fasting blood sugar was 224 mg. per 100 cc. Her subsequent course is given in Table 1:*

TABLE 1

CASE I. A. BA., FEMALE, COLORED, AGED FORTY-FOUR, HEIGHT 60½ INCHES.
IDEAL WEIGHT: 131 POUNDS, 25 PER CENT OVERWEIGHT

Date, 1939.	Weight, lbs.	Diet.			Glycosuria, %.	Blood sugar, mg. per 100 cc.
		Protein.	Carbohydrate.	Calories.		
January 27	163¾	80	130	1500	1.4	224
February 10	163½	80	130	1500	1.4	345
February 24	161½	80	130	1500	0	186
March 24	156½	80	130	1500	0	104
April 7	155¾	80	130	1500	0	92
April 21	156	80	130	1500	0	107
May 19	151¾	80	130	1500	0	106

Comment.—This patient's dextrose tolerance curve was normal in September, 1937, when she weighed 145 pounds. Sixteen months later, with a weight gain of 18 pounds, she was definitely diabetic. With weight reduction the blood sugar fell fairly promptly to normal.

Cases II, III and IV.—These cases (Tables 2, 3 and 4) will illustrate the control of diabetes in obese patients with loss of weight.

* In all of the tables, the blood sugar values are fasting values (*i. e.*, the blood specimens were taken at least fourteen hours after a meal, unless otherwise stated). The determinations were made by the Folin-Wu method. Protamine zinc insulin is represented by the use of parentheses; otherwise, unmodified insulin is indicated. The number of grams of fat in the diet is sufficient in each case to make up the stated number of calories, on the basis of 1 Gm. of fat furnishing 9 calories.

TABLE 2

CASE II. M. HO., FEMALE, COLORED, AGED FORTY-ONE, HEIGHT 65 INCHES.
IDEAL WEIGHT: 143 POUNDS, 56 PER CENT OVERWEIGHT

Date.	Weight, lbs.	Diet.			Glyco- suria.	Blood sugar, mg. per 100 cc.
		Protein.	Carbohy- drate.	Calories.		
September 30, 1937	223	75	90	1200	4+	366
October 7	220	75	90	1200	4+	240
October 28	214	75	90	1200	0	160
November 11	208½	75	90	1200	0	133
December 9	202½	75	90	1200	0	110
February 10, 1938	187	75	90	1200	0	130
April 7	180	75	90	1200	0	120
July 7	171½	75	90	1200	0	111
September 29	164½	75	90	1200	0	102
December 8	171	75	90	1200	0	146
January 5, 1939	168	75	90	1200	0	96
March 30	169	75	90	1200	0	120

TABLE 3

CASE III. A. BU., FEMALE, WHITE, AGED FORTY-EIGHT, HEIGHT 60½ INCHES.
IDEAL WEIGHT: 132 POUNDS, 40 PER CENT OVERWEIGHT

Date.	Weight, lbs.	Diet.			Glyco- suria.	Blood sugar, mg. per 100 cc.
		Protein.	Carbohy- drate.	Calories.		
December 3, 1934	185	70	100	1200	0	231
December 14	181½	70	100	1200	0	150
February 15, 1935	171½	70	100	1200	0	135
March 8	167	70	100	1200	0	128
June 28	153	80	120	1500	0	112
November 1	150	80	120	1500	0	108
April 3, 1936	151	80	140	1600	0	104
November 27	155	80	140	1600	0	117
July 16, 1937	154½	80	140	1600	0	104
November 5	153	80	140	1600	0	104
May 20, 1938	158½	80	140	1600	0	119
October 14	160½	80	140	1600	0	113
January 20, 1939	161½	80	140	1600	0	122
March 31	163½	80	140	1600	0	142

TABLE 4

CASE IV. E. B., FEMALE, WHITE, AGED FORTY-FIVE, HEIGHT 60½ INCHES. IDEAL
WEIGHT: 132 POUNDS, 61 PER CENT OVERWEIGHT

Date.	Weight, lbs.	Diet.			Glyco- suria, %.	Blood sugar, mg. per 100 cc.
		Protein.	Carbohy- drate.	Calories.		
July 23, 1937	212	65	90	1200	0.5	200
July 30	207	65	90	1200	0	141
August 6	205½	65	90	1200	0	103
September 10	192	65	110	1300	0	103
October 29	180½	75	125	1400	0	96
December 17	175½	75	125	1400	0	95
March 25, 1938	170½	75	125	1400	0	95
July 29	168½	75	125	1400	0	86
October 21	173½	75	125	1400	0	97
December 30	174	75	125	1400	0	106
February 10, 1939	173½	75	125	1400	0	102
March 10	172½	75	125	1400	0	94

Comment.—In these three cases, adherence to a low caloric diet with loss of weight resulted in prompt control of the diabetes.

Case V.—This case illustrates: (1) the development of diabetic coma in an obese patient, (2) eventual control of the diabetes (after recovery from coma) by weight reduction, and without the use of insulin.

This patient was admitted to the Pennsylvania Hospital on April 24, 1938, in diabetic coma. Diabetes had not been diagnosed prior to this time. On admission, the blood sugar was 520 mg. per 100 cc., and the carbon dioxide combining power of the plasma was 11 volumes per cent. Under appropriate treatment, including 280 units of unmodified insulin during the first day and 138 units the second day, the acidosis was soon abolished and the blood sugar reduced. Her subsequent course is charted in the following table (Table 5). From May 19, 1938 on, the patient was seen in the out-patient clinic.

TABLE 5

CASE V. M. HE., FEMALE, COLORED, AGED THIRTY-EIGHT, HEIGHT 61 INCHES.
IDEAL WEIGHT: 137 POUNDS, 45 PER CENT OVERWEIGHT

Date.	Weight, lbs.	Diet.			Insulin, units.	Glyco- suria.	Blood sugar, mg. per 100 cc.
		Pro- tein.	Carbo- hy- drate.	Cal- ories.			
April 29, 1938	.	75	125	1200	25-15-25-10	4+	224
May 3	.	75	125	1200	25-20-32-18	2+	180
May 6	199	75	125	1200	28-18-30-20	0	206
May 9	195	75	125	1200	28-18-30-20	0	156
May 12	.	75	125	1200	26-16-28-18	0	130
May 19	185	75	125	1200	26-14-25-15	0	129*
June 16	184	75	125	1200	20-8-18	0	104*
July 7	183	75	125	1200	10-0-8	0	94*
August 18	172	75	125	1200	5-0-3	0	108*
September 2	174	75	125	1200	0	0	132
September 29	169	75	125	1200	0	0	90
November 17	165	75	125	1200	0	0	101
January 19, 1939	161	75	125	1200	0	0	89
March 23	164	75	125	1200	0	0	102

* These blood sugar determinations were made on blood taken about 1 hour after the patient had eaten breakfast, and 1½ hours after taking the morning dose of insulin.

Comment.—Even though this patient's diabetes when untreated was severe enough to result in coma, she needed gradually decreasing doses of insulin for only four months after the development of acidosis. During this time, her weight was reduced from 199 pounds to 174 pounds by means of a low-caloric diet. Subsequently, her diabetes has been well controlled without insulin, but with further weight reduction.

Case VI.—This case will show lack of control of diabetes in an obese patient when the weight is maintained (Table 6).

TABLE 6

CASE VI. M. E., FEMALE, WHITE, AGED FIFTY, HEIGHT 63 INCHES. IDEAL WEIGHT: 141 POUNDS, 27 PER CENT OVERWEIGHT

Date.	Weight, lbs.	Diet.			Glycosuria, %.	Blood sugar, mg. per 100 cc.
		Protein.	Carbohydrate.	Calories.		
July 8, 1938	179½	75	100	1200	2.0	240
July 15	178½	75	100	1200	1.4	251
July 22	178¾	75	90	1000	1.1	262
August 19	172½	75	90	1000	0.3	169
October 28	177½	75	90	1000	v.ft.trace	150
December 30	183¾	75	90	1000	0	186
January 20, 1939	184	75	90	1000	0	197
February 10	186¾	75	90	1000	0	190

Comment.—With failure to follow a low-caloric diet, this patient's blood sugar remained high. If she continues to exceed her prescribed diet, insulin will be needed to control the diabetes, and undoubtedly large doses will be necessary for complete control.

Case VII.—This case illustrates: (1) failure of control of diabetes with maintenance of obesity; (2) control of diabetes with loss of weight; and (3) subsequent lack of control, even with insulin, with return of the obesity (Table 7).

Comment.—With failure to lose weight when first treated in the out-patient clinic, this patient's blood sugar stayed high. While under more careful supervision in the hospital, she lost weight and her blood sugar fell to normal. Later, with a gain in weight after she returned home, her diabetes has been poorly controlled even with moderate doses of insulin.

Discussion.—By these seven illustrative cases of obese diabetic patients, we have brought out the following facts: (1) weight reduction by means of a low-caloric diet in an uncomplicated, adult obese diabetic patient will result in a fall in the blood sugar level to normal; (2) when an obese diabetic patient gains weight, there is an increase in the apparent severity of the diabetes; and (3) if a diabetic patient remains obese, complete control of the diabetes is difficult, even with large doses of insulin.

TABLE 7

CASE VII. E. M., FEMALE, WHITE, AGED FIFTY-FOUR, HEIGHT 58½ INCHES.
IDEAL WEIGHT: 129 POUNDS, 15 PER CENT OVERWEIGHT

Date.	Weight, lbs.	Diet.			Insulin, units.	Glyco- suria, c.c.	Blood sugar, mg. per 100 cc.
		Pro- tein.	Carbo- hy- drate.	Cal- ories.			
October 6, 1933	148	70	80	1200	0	not done	280
October 27	146½	70	75	1100	0	2.0	249
November 3	147	70	70	1000	0	1.0	209
December 8	146½	70	70	1000	0	0	180
March 2, 1934	134	70	120	1500	0	0	125
June 8	146½	70	100	1200	0	0	185
October 5	151½	70	85	1000	0	0	258
March 25, 1935	147½	70	85	1000	0	0	234
September 13	150½	70	85	1000	0	0	181
January 10, 1936	145½	70	85	1000	10-0-8	0	221
November 13	150	70	85	1000	10-0-10	0	180
March 5, 1937	150½	70	130	1200	(15)-0-0	ft. pos.	217
September 17	150	70	130	1200	(20)-0-0	0.8	265
October 8	151	70	130	1200	(30)-0-0	0	223
March 4, 1938	158½	70	120	1200	(32)-0-0	0	154
September 20	152	70	120	1200	(32)-0-0	1.0	190
January 20, 1939	153½	70	120	1200	(32)-0-0	0	180
March 3	151½	70	120	1200	(34)-0-0	0	200

* Between these two visits to the Out-Patient Department, the patient had been admitted to the hospital because of precordial pain. The weight loss in the hospital was obviously due to closer dietary supervision than was possible when the patient was at home. Her diet in the hospital was: protein, 70 Gm.; carbohydrate, 125 Gm.; fat, to make 1000 calories, until January 15, 1934. From then on it was: protein 70, carbohydrate 120, 1500 calories. With the loss in weight from 146 pounds to 134 pounds, the blood sugar fell to normal.

Aside from its bad effect on the diabetes, obesity in these patients is undesirable for other reasons: The adverse effects of obesity on such degenerative processes as hypertensive cardiovascular disease and osteo-arthritis are well known. Since weight reduction in itself is beneficial, and since it accomplishes the same results as large doses of insulin, it seems to us to be the treatment of choice in the obese diabetic patient.

TREATMENT OF THE THIN DIABETIC PATIENT

Here the problem is the direct opposite of that of the fat diabetic. The thin diabetic must gain weight and usually needs large doses of insulin to bring this about. The question might be asked, what do we mean by a thin diabetic? That could be answered roughly by stating that a diabetic is considered thin if he is 15 per cent or more under the ideal weight for his age, sex and height. By restoring the thin diabetic to his ideal weight, his general health is also restored, and conse-

quently many serious and undesirable complications of diabetes are avoided.

As already mentioned, most thin diabetics need at least 30 to 35 calories per kilogram of the ideal weight to bring about an adequate gain in weight. The protein requirement will vary considerably with the condition of the patient; however, between $\frac{2}{3}$ and $1\frac{1}{2}$ Gm. per Kg. should be available in the diet for the adult, and $1\frac{1}{2}$ to 3 Gm. per Kg. for the child. These patients require an amount of carbohydrate varying from 150 to 300 Gm. per diem. The balance of the total calories is made up in fat. If the calculated diet does not result in a gain in weight after a reasonable time has been allowed for control of hyperglycemia and glycosuria, then by all means the total calories should be increased until the patient shows a very definite tendency to gain weight. It should be emphasized that rule of thumb does not always apply. Each patient is an individual, and individual treatment is necessary.

A word about the measurement of the diet by the patient: There seems to be a prevalent idea that all patients with severe diabetes should weigh their food. This is true for a certain small percentage, but in the main, it is not necessary; in fact in the long run the patient will cooperate better if he is not subjected to this great inconvenience. A strict adherence to household measures in most instances will suffice. This is especially true since the introduction of protamine zinc insulin.

Insulin: Kind, Amount and Distribution.—As to the kind of insulin, much may be said, but most diabetics will do well on protamine zinc insulin alone or with a small supplementary dose of unmodified insulin, leaving only a relatively small percentage who must use multiple doses of the unmodified insulin. In certain patients the single dose of protamine zinc insulin must be supplemented by unmodified insulin to avoid either a glycosuria in the late morning or early afternoon hours resulting from too small an amount of protamine insulin, or the hypoglycemia seen so often in the early morning hours resulting from too large an amount of protamine insulin. The crystalline insulin appears to have no particular advantage over unmodified insulin in regard to prolonged or delayed activity. Regardless of whether the new or old type of insulin is used alone or in combination, the thin diabetic patient will

usually require large amounts to insure adequate control, that is, a normal fasting blood sugar, sugar-free urine throughout the twenty-four hours, and the maintenance of weight at or a trifle below the standard for the age, height and sex of the patient.

We shall now present illustrative cases, showing the methods and results of treatment in various thin diabetic patients:

Case VIII.—This patient had a classical onset of diabetes in January, 1938 (increased hunger, thirst and polyuria) and lost approximately 20 pounds in three months. Due to extreme nervousness associated with this weight loss, her basal metabolic rate was determined and found to be normal. After four months of treatment she was markedly improved and her weight increased steadily to 118 pounds. Her course is shown in Table 8.

TABLE 8

CASE VIII. G. A., FEMALE, WHITE, AGED TWENTY-FOUR, HEIGHT 62 INCHES.
IDEAL WEIGHT: 121 POUNDS, 15 PER CENT UNDERWEIGHT

Date.	Weight, lbs.	Diet.			Insulin.	Glyco- suria.	Blood sugar, mg. per 100 cc.
		Pro- tein.	Carbo- hy- drate.	Cal- ories.			
April 7, 1938	103	85	150	1620	(20)-0-0	4+	340
April 11	102	85	150	1620	(28)-0-0	4+	240
April 15	104½	85	150	1620	(30)-0-0	3+	210
April 19	105½	85	150	1620	6 (32)-0-0	3+	205
April 26	108	85	150	1620	4 (35)-0-0	2+	198
May 3	109	85	150	1620	4 (35)-0-0	0	96
May 17	111	85	150	1620	5 (35)-0-0	0	106
June 1	113	85	150	1620	4 (38)-0-0	0	174*
June 14	116	85	150	1620	5 (38)-0-0	0	91
July 5	117½	85	150	1620	5 (38)-0-0	0	89
July 26	117	85	150	1620	(42)-0-0	0	150
August 10	118	85	150	1620	(40)-0-0	0	87

* The patient did not follow her diet for one day preceding this determination.

Case IX.—This patient had an acute onset of diabetes during an attack of mumps in 1936; he dropped from a normal weight of 160 pounds to 140 pounds. After several years of rather indifferent treatment—following a vague sort of dietary

restriction and taking 10 units of insulin night and morning, during which time he rarely saw a physician—he decided to check up on his general condition. In November, 1938, he was placed on a strict diet and took 25 units of protamine zinc insulin. The following week he developed a severe upper respiratory infection, but refused to be hospitalized because he had been on a new job only a few days. The seriousness of the situation was carefully explained to him. For three weeks things progressed very poorly, as can be seen from Table 9.

TABLE 9

CASE IX. A. Q., MALE, WHITE, AGED TWENTY-NINE, HEIGHT 71 INCHES. IDEAL WEIGHT: 165 POUNDS, 19 PER CENT UNDERWEIGHT

Date.	Weight, lbs.	Diet.			Insulin.	Glycosuria.	Blood sugar, mg. per 100 cc.
		Protein.	Carbohydrate.	Calories.			
November 20, 1938	142	85	150	2000	(25)—0-0	4+	330
November 24	142	85	150	2000	(30)—0-0	4+	
November 28	140	85	150	2000	(35)—0-0	4+	286
December 2	139½	85	150	2000	(40)—0-0	4+	192
December 7	136	85	150	2000	(46)—0-0	4+	
December 11	135	85	150	2000	(52)—0-0	4+	340
December 14	134	85	150	2000	(56)—0-0	4+	
December 18	133	85	150	2000	{(60)—0-0 10—0-0	4+	320
December 23	135	100	200	2325	(66)—0-0	2+	78
January 3, 1939	136	100	200	2325	(66)—0-0	1+	70
January 17	139½	100	200	2325	(66)—0-0	0	80
February 7	140	100	200	2325	(72)—0-0	1+	160
February 21	143½	100	200	2325	(74)—0-0	1+	140
March 14	147	100	200	2325	(74)—0-0	0	115
April 4	152½	100	200	2325	(74)—0-0	0	96
April 17, 1939	155	100	200	2325	(74)—0-0	0	100

The upper respiratory infection did not subside until after the insulin was considerably increased. The blood sugar remained high, the glycosuria continued unabated and he lost weight at an alarmingly steady rate. When the upper respiratory infection subsided, the blood sugar came down to normal, the urine became sugar free, and the weight showed a consistent upward trend. In accomplishing all this the diet had been increased to 2325 calories, and the insulin requirement reached 74 units for twenty-four hours.

Case X.—This woman came into the Clinic in a very marked state of undernutrition, but refused to enter the hospital. However, since she had no obvious complications she

was seen in the Out-Patient Department. Most of the time we were unable to obtain fasting blood sugars, and the non-fasting blood sugars were not particularly good at first, but the last six months of her record shows good control. This case brings out several points very clearly: (1) that she needed large doses of insulin, and (2) that she gained a total of 30 pounds. Another interesting thing is that such a severe diabetic was handled as an out-patient without any difficulty—a fact which should be a source of encouragement for many physicians faced with the same problem in isolated districts where hospital facilities are not available (Table 10).

TABLE 10

CASE X. M. L., FEMALE, WHITE, AGED FIFTY-SIX, HEIGHT 64 INCHES. IDEAL WEIGHT: 144 POUNDS, 33 PER CENT UNDERWEIGHT

Date.	Weight, lbs.	Diet.			Insulin.	Glyco-suria.	Blood sugar, mg. per 100 cc.
		Pro-tein.	Carbo-hy-drate.	Cal-ories.			
October 25, 1937	96	80	150	1820	(20)-0-0	1+	280
November 11	100	80	150	1820	(28)-0-0	1+	280*
December 2	104	80	150	1820	(38)-0-0	0	290*
December 23	110	80	150	1820	(50)-0-0	0	204*
January 20, 1938	112	80	150	1820	(50)-0-0	0	280*
February 24	113	80	150	1820	(50)-0-0	0	280*
March 24	116	80	150	1820	(50)-0-0	1+	225*
April 28	114	80	150	1820	(56)-0-0	2+	346*
May 12	115	80	150	1820	(58)-0-0	0	224*
June 2	115	80	150	1820	(62)-0-0	0	218*
June 30	116	80	150	1820	(64)-0-0	0	220*
September 1	118	80	150	1820	(64)-0-0	0	202*
October 6	123	80	150	1820	(64)-0-0	0	91
November 10	121	80	150	1820	(66)-0-0	0	180*
December 8	124	80	150	1820	(66)-0-0	0	186*
January 12, 1939	125	80	150	1820	(66)-0-0	0	140*
February 9	124	80	150	1820	(64)-0-0	0	147*
March 9	123	80	150	1820	(64)-0-0	0	96
April 6	126	80	150	1820	(62)-0-0	0	60

* These blood sugar determinations were made on blood taken 1½ hours after the patient had eaten breakfast and taken insulin.

Case XI.—This very undernourished patient was admitted to the hospital on September 24, 1937, with vaginal bleeding from an incomplete abortion. Diabetes had not been diagnosed prior to her admission, when a fasting blood sugar of 372 mg. per 100 cc. was discovered. A dilatation and evacuation of the uterus was done on the day of admission. Her further course is given in Table 11. From November 26, 1937, on, she was followed in the Out-Patient Clinic.

TABLE 11

CASE XI. L. S., FEMALE, COLORED, AGED FORTY-FIVE, HEIGHT 65½ INCHES
IDEAL WEIGHT: 147 POUNDS, 33 PER CENT UNDERWEIGHT

Date.	Weight, lbs.	Diet.			Insulin.	Glyco- suria.	Blood sugar, mg. per 100 cc.
		Pro- tein.	Carbo- hy- drate.	Cal- ories.			
September 28, 1937	70	150	1400	78 (total)	4+	372
October 5	98½	70	150	1400	(36)-0-0	1+	146
October 17	100	70	150	1400	16-8-12	0	130
November 11	101	70	150	1400	(28)-0-0	0	166
November 26	100	70	200	2000	(28)-0-0	0	144
January 21, 1938	99	70	200	2000	(30)-0-0	0	169
February 18	100	70	200	2200	(30)-0-0	0	108
April 15	104	70	200	2200	(34)-0-0	0	165
June 17	108½	90	200	2200	(32)-0-0	0	86
August 26	109½	90	200	2200	(34)-0-0	0	123
October 21	111	90	200	2200	(24)-0-0	0	80
December 16	115	90	200	2200	(30)-0-0	0	123
February 3, 1939	114	90	200	2200	(30)-0-0	0	148
March 3	117½	90	200	2200	(34)-0-0	0	123
April 14	121	90	200	2200	(32)-0-0	0	118

Comment.—With moderate doses of insulin, and a diet furnishing 33 calories a day per Kg. of ideal weight, the diabetes of this very undernourished patient has been well controlled and she is gaining weight slowly but steadily.

SAMPLE DIETS

In order to give a clearer idea of the diets we are prescribing for fat and thin diabetics, we are tabulating a typical low-caloric diet for a fat diabetic patient, consisting of protein, 70 Gm.; carbohydrate, 100 Gm.; fat, 58 Gm., and totaling 1200 calories. A typical high-caloric diet for a thin diabetic patient consists of: protein, 85 Gm.; carbohydrate, 200 Gm.; fat, 118 Gm.; and totals 2200 calories. A list of the various vegetables and fruits used in these diets is included. These are grouped according to the percentage of carbohydrate they contain.

We want to emphasize again that, while these two diets are fairly representative, each patient presents a different problem and individual diet prescriptions are essential.

Diet Containing P 85, F 118, C 200, Calories 2200

Food	Gm.	Approximate Household Measures	Calories		
			P.	F.	C.
<i>Breakfast</i>					
12% fruit	100	1 medium orange			12
Eggs	100	2	14	10	
Cereal, cooked	120	$\frac{1}{4}$ cup	3		16
Bread	60	2 slices	6		32
Milk	120	$\frac{1}{4}$ cup	3.5	5	6
Coffee cream (20%)	60	$\frac{1}{4}$ cup	2	12	2
Butter	15	1 level tablespoonful		13	
			28.5	40	68
<i>Lunch</i>					
Meat	30	1 ounce (1 medium lamb chop)	7	5	
3% vegetable	300	3 servings, $\frac{1}{2}$ cup each	6		9
18% fruit	65	$\frac{1}{4}$ medium banana			12
Bread	60	2 slices	6		32
Milk	240	1 cup	7	10	12
Coffee cream	60	$\frac{1}{4}$ cup	2	12	2
Butter	15	1 level tablespoonful		13	
			28	40	67
<i>Dinner</i>					
Meat	45	1 $\frac{1}{2}$ ounces (small ham-burger)	10.5	7.5	
3% vegetable	100	$\frac{1}{2}$ cup	2		3
9% vegetable	100	$\frac{1}{2}$ cup	3		9
18% vegetable	100	1 medium potato	5	1	18
9% fruit	135	$\frac{1}{4}$ grapefruit			12
Bread	30	1 slice	3		16
Milk	120	$\frac{1}{4}$ cup	3.5	5	6
Coffee cream	60	$\frac{1}{4}$ cup	2	12	2
Butter	15	1 level tablespoonful		13	
			29.0	38.5	66
Total			85.5	118.5	201

Diet Containing P 70, F 58, C 100, Calories 1200

Food	Gm.	Approximate Household Measures	Calories		
			P.	F.	C.
<i>Breakfast</i>					
12% fruit	100	1 medium orange			12
Eggs	100	2	14	10	
Cereal, cooked	120	$\frac{1}{4}$ cup	3		16
Milk	120	$\frac{1}{4}$ cup	3.5	5	6
Coffee cream (20%)	20	1 $\frac{1}{4}$ tablespoonsful	.7	4	.7
			21.2	19	34.7
<i>Lunch</i>					
Meat	45	1 $\frac{1}{2}$ ounces (1 small ham-burger)	10.5	7.5	
3% vegetable	300	3 servings ($\frac{1}{4}$ cup each)	6		9
18% fruit	65	$\frac{1}{4}$ medium banana			12
Skim milk	240	1 cup	7		12
Butter	15	1 level tablespoonful		13	
			23.5	20.5	33

Dinner

Meat	75	2½ ounces (1 average slice roast beef)	17.5	12.5	
6% vegetable	100	½ cup	2		6
9% vegetable	100	½ cup	3		9
9% fruit	135	½ grapefruit			12
Skim milk	120	½ cup	3.5		6
Butter	10	2 level teaspoonsful		8.5	
			26.0	21.0	33
		Total	70.7	60.5	100.7

The Carbohydrate Percentage of Common Fruits and Vegetables

3 per cent	6 per cent	9 per cent
<i>Vegetables</i>	<i>Vegetables</i>	<i>Vegetables</i>
Asparagus, fresh or canned	Beans, scarlet runner	Artichokes
Beans, green, wax, fresh or canned	Beans, snap	Beets
Beet greens	Beets, canned	Brussels sprouts
Broccoli	Chives	Carrots
Cabbage	Collards	Onions
Cauliflower	Dandelion greens	Peas, very young
Celery	Eggplant	Peas, canned
Chard	Kohlrabi	Rutabagas
Cucumbers	Okra	
Endive	Peppers	<i>Fruits</i>
Lettuce	Squash, winter	Blackberries
Mustard greens	Tomato, pureed, canned	Cranberries
Radishes	Turnips	Currants
Sauerkraut, fresh or canned	<i>Fruits</i>	Grapefruit
Spinach	Blackberry juice	Grapefruit juice
Squash, summer	Muskmelon, including cantaloups and honeydew	Lemons
Tomatoes, fresh or canned	Strawberries	Lemon juice
Turnip tops	Watermelon	Loganberry juice
Watercress		Tangerines
<i>Fruits</i>		
Rhubarb		
12 per cent	15 per cent	18 per cent
<i>Vegetables</i>	<i>Vegetables</i>	<i>Vegetables</i>
Beans, lima, canned	Corn, green, very young	Beans, baked
	Parsnips	Beans, kidney (red) cooked
<i>Fruits</i>	Peas, medium	Corn, canned
Apple juice	Salsify	Potatoes
Apricots		Succotash, canned
Cherries, sour	<i>Fruits</i>	
Oranges	Apples	<i>Fruits</i>
Orange juice	Blueberries	Cherries, sweet
Peaches	Grapes	Crabapples
Peach juice	Pears	Figs
Pineapple		Grapejuice, unsweetened
Pineapple juice (fresh)		Bananas
Plums (excluding prunes)		
Raspberries		

SUMMARY

We have attempted to show the differences in the treatment of fat and thin diabetic patients. These differences are summarized below, and other cases besides those given previously are included. It should be emphasized that these results are typical of results obtained in a larger number of overweight and underweight diabetic patients who have cooperated in following the prescribed treatment.

Overweight Patients

Patient.	Initial weight, lbs.	Initial blood sugar, mg. per 100 cc.	Per cent overweight.	Weight loss, lbs.	Calories in diet.	Insulin requirement.
A. Be	163 ³ / ₄	224	25	12	1500	0
M. H.	223	366	56	58 ¹ / ₂	1200	0
A. Ba.	185	231	40	35	1200	0
E. B.	212	200	61	43 ¹ / ₂	1200	0
R. R.	185	264	39	30 ¹ / ₂	1200	0
K. F.	207	300	48	27	1200	0
A. Fe.	188	250	39	41	1100	0
D. D.	186	238	49	35	1100	0
A. Fr.	205	225	46	23	1200	0

Underweight Patients

Patient	Initial weight, lbs.	Initial blood sugar, mg. per 100 cc.	Per cent underweight.	Weight gain, lbs.	Calories in diet.	Daily insulin requirement.
G. A.	103	340	15	16	1620	(40)
A. Q.	142	330	19	22	2325	(74)
M. L.	96	280	33	30	1820	(64)
L. S.	98 ¹ / ₂	372	33	23 ¹ / ₂	2200	(32)
F. S.	94	169	22	18	1700	36
D. B.	118	193	14	13	2400	(12)
T. H.	131	280	16	19	2400	63
M. S.	120	265	16	24	2000	(24)
E. G.	115	200	12	9	1600	(28)

To recapitulate, the initial blood sugar level alone is not an index of the severity of the diabetes. This may be as high, or even higher, in an obese patient whose diabetes is actually mild as in a thin patient, whose diabetes is severe. The underweight diabetic patient, who needs to gain weight, practically always needs insulin in order to control his diabetes. The overweight uncomplicated diabetic patient, on the other hand, can usually be controlled by means of a low caloric diet, and without the use of insulin. Aside from avoiding the use of insulin when this is not needed, the loss of weight in these patients is in itself desirable.

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CLINIC OF DR. TRACY D. CUTTLE

PENNSYLVANIA HOSPITAL

DIABETES MELLITUS IN CHILDHOOD AND ADOLESCENCE

DIABETES MELLITUS in childhood and adolescence differs in several important aspects from the disease in adults:

1. *The onset is abrupt and violent.* Joslin¹ has analyzed the histories of a series of diabetic children and has been able to date the onset of the disease within a period of two months in 44 per cent of the cases in his clinic.

2. *It is a more severe disease than it is in adults.* All children suffering from diabetes require insulin.^{2, 3, 4, 5} Of our adult patients, only 25 to 35 per cent require insulin.⁶

3. *The disease is usually progressive.* "Growth and development may account for progress in severity of diabetes in youth. Increasing quantities of food are demanded, greater heat is produced, greater activity of the reproductive glands takes place, and in the case of the anterior pituitary, besides providing growth, it may also furnish a diabetic substance."⁷

4. *The disease is more labile in children than it is in adults.* There is frequently a "facile replacement of controlled diabetes by acidosis or hypoglycemia."^{7, 8} White⁷ accounts for this lability of the disease in childhood by the greater activity of the child and the relatively small glycogen reserve which the child possesses.

5. *There is a more definite relationship between juvenile diabetes and hyperfunction of the anterior lobe of the hypophysis than is the case in adults.*⁵

6. *The hereditary factor* probably accounts for a larger proportion of juvenile than adult cases of diabetes.^{1, 9, 10} In a

series of 553 children from the George F. Baker Clinic, 39 per cent gave a family history of diabetes; 44 per cent of the Jewish children in the same series were considered to be "hereditary diabetics."¹

7. *It is uncommonly preceded by obesity or degenerative changes*, which often foreshadows the onset of diabetes in adults.⁹

8. *There is more difficulty in maintaining a strict dietary regulation in children than in adults.*⁹

The following case illustrates how these differences manifest themselves clinically in a child suffering from diabetes mellitus:

Case I.—G. D., a white female aged fourteen years. Weight 123 pounds (55.9 Kg.), height 66 inches (167.6 cm.).

The patient was first admitted to the Pennsylvania Hospital on February 19, 1934, when she was eight years of age. She had enjoyed good health until three weeks before admission when there was such a marked increase in the frequency of urination that within two weeks she was voiding every twenty minutes, day and night. She also developed a ravenous appetite and a great thirst. "The urine was syrupy and, when it dried on her clothing, left a crisp area." She lost 8 pounds in two weeks and at the time of admission weighed 60 pounds (27.2 Kg.) and measured 54 inches (137 cm.) in height. None of her relatives had diabetes.

The child was tall and thin and lay comfortably in bed in no apparent discomfort. Her face was flushed and her skin and mucous membranes were dry. There was a slight odor of acetone on her breath. Respirations were not increased either in rate or depth. Her tonsils were enlarged and inflamed. No further significant abnormalities were noted on physical examination.

Her urine was concentrated (specific gravity 1.045) and completely reduced Benedict's solution. Acetone and diacetic acid were present. The blood sugar was 230 mg. per 100 cc. and the carbon dioxide combining power of the blood plasma was 38 volumes per cent.

The following diet was prescribed: Carbohydrate 110 Gm.; protein 45 Gm.; and fat 53 Gm. (1100 calories). This was divided into three equal meals. Four injections of unmodified insulin a day (16 units before breakfast, 14 units at 11:30 a.m., 16 units before dinner, and 10 units at midnight) were required to control the glycosuria, ketonuria, and hyperglycemia.

Before the patient left the hospital the diet was increased to 1500 calories because of her failure to gain weight. It has been altered frequently during the five years she has been under our care in the clinic and the hospital (Table 1). One admission was necessitated by a mild dietary indiscretion, which resulted in ketosis, and three were for readjustment to new forms of insulin and for further investigation. She has attended the clinic at intervals of from one to three weeks during this entire period (Fig. 92).

The record of this girl's first five years as a diabetic patient illustrates seven of the eight ways already mentioned in

which juvenile diabetes differs from the disease in adults. A family history of diabetes is lacking, but one of her immediate

TABLE 1

FIGURES OBTAINED FROM THE RECORD IN CASE I AT INTERVALS OF THREE MONTHS FOR A PERIOD OF FIVE YEARS

Date.	Age, yrs.	Ht., in.	Wt., lbs.	Diet.				Insulin, units.	Urine, % sugar.	Blood.	
				P.*	C.*	F.*	Cal.			Sugar.†	Chol.†
1934											
Mar. 27	8	54	61	60	120	86	1500	0%	neg.	112	200
Jun. 22	9	55	65	65	130	100	1700	0%	neg.	129	
Sep. 21	67	70	140	115	1900	12-0-8	neg.	239*	
Dec. 21	75	70	140	115	1900	14-4-12-10	neg.	250*	
1935											
Mar. 22	77	70	140	85	1700	27-10-23-8	neg.	100	190
Jun. 7	10	56	81	70	140	85	1700	26-10-22-11	neg.	163	
Sep. 27	82	70	140	85	1700	22-13-0-23	neg.	247*	
Dec. 20	86	70	140	85	1700	21-13-19-8	neg.	226*	
1936											
Mar. 9	87	70	140	85	1700	19-11-19-6	neg.	126	190
Jun. 26	11	60	90	70	140	85	1700	16-11-8-8	1	234*	
Sep. 25	91	70	140	85	1700	32 24	neg.	286*	
Dec. 18	88	70	200	102	2000	43 40	0.7	240*	
1937											
Mar. 26	92	70	200	102	2000	72 20-0-8	1.6	107	173
Jun. 25	12	63	89	80	250	131	2500	72 3-0-12	3.0	183	
Sep. 17	89	80	250	131	2500	72 8-0-16	neg.	132	
Dec. 24	94	95	250	180	3000	76 10-0-24	3.0	231	
1938											
Mar. 25	103	95	250	180	3000	80 10-0-10	2.0	324*	173
Jun. 17	13	65	111	95	250	180	3000	84 50-0-24	neg.	74	
Sep. 23	115	95	250	180	3000	88 46-0-32	1.4	120	
Dec. 16	117	95	250	180	3000	90 46-0-30	1.5	282	
1939											
Mar. 10	121	95	250	147	2700	106 46-30	2.5	105*	173
Jun. 2	14	66	123	95	250	124	2400	120 40-10	neg.	167	

* Gm.

† mg./100 cc.

‡ Reference 11 (Case 6).

§ Blood taken $\frac{1}{2}$ hour after breakfast and insulin.

○ Protamine insulin.

● Crystalline insulin.

□ Protamine zinc insulin.

Note: Since 1937 the insulin for this patient has been donated by Sharp & Dohme of Philadelphia.

family may yet develop diabetes as it is not unusual for the disease to appear in the child before it is noted in the parent.⁷



Fig. 92.—Photograph of G. D. (Case I) taken June 2, 1939, five and one-half years after the onset of diabetes. It may be noted that she is a well developed and well nourished girl of fourteen although she requires 170 units of insulin a day to control her diabetes.

DIAGNOSIS

Many authors have stressed the difficulty of making a diagnosis of diabetes mellitus in childhood.^{4, 7, 12, 13} "Often the first recognition is made in chemical coma, and the younger the patient the more striking is the fact."¹⁴ The symptoms of juvenile diabetes are in most cases the classical polyuria, polydipsia, polyphagia, and loss of weight. In infancy the disease is rare, but the possibility of diabetes mellitus should be remembered in any thirsty and marasmic baby.

The diagnosis of diabetes is made on the basis of a per-

sistent glycosuria and hyperglycemia. Some authors believe that a level for the fasting blood sugar above 140 mg. per 100 cc. indicates diabetes.^{7, 12} The disease in childhood is usually so severe, however, that no artificial yardstick is necessary to make a diagnosis. Sugar in the urine of a child should not be dismissed lightly. Joslin¹ found that of a group of children showing sugar in the urine, 80 per cent had true diabetes and only 0.9 per cent had renal glycosuria. The final diagnosis rests upon the level of the blood sugar. Sugar tolerance tests are rarely necessary, but they are indicated if the urine contains sugar and random determinations of the blood are normal. White⁷ found that the normal child tolerated 1.8 Gm. of dextrose per Kg. of body weight, and we have adopted this value for our test dose.

TREATMENT

Just as the disease in childhood differs in several important aspects from the disease in adults, so the treatment must be varied to take account of these differences.

The essentials of correct treatment are *insulin, diet, exercise, and education*. The treatment should be so conducted that the following standards for controlled diabetes are fulfilled:

1. *Adequate nourishment.*
2. *A level of the blood sugar below 200 mg. per 100 cc.*
3. *Glycosuria less than 10 Gm. of glucose in twenty-four hours.*
4. *Cholesterol content of the blood below 230 mg. per 100 cc.*
5. *A normal psychologic adjustment and development.*

The first four criteria are generally agreed upon, but the last is equally important and is frequently neglected.

To attain these desired results two phases of treatment must be considered: (1) initial adjustment, and (2) periodic readjustment to allow for growth and development. Furthermore, one must contend with the greater physiologic and emotional instability of the child. "There can be no pattern of treatment applicable for all cases. There can be no constant pattern for the same patient day in and day out, for the regimen of the individual day governs the diabetic schedule."² No

general diet can be given for a particular age, nor can the amount of insulin be estimated for a particular weight.¹⁴

The following program may be used as a basis for starting treatment. Frequent adjustments will have to be made to suit the individual patient. The initial treatment of children should be carried out in the hospital. This period of institutional care is important, for it not only supplies the facilities for adequate investigation, but it allows for a period of supervised instruction. The education of the child is one of the primary principles of treatment.

Diet.—The diet is relatively constant in comparison with the other factors in the management of a diabetic child. The standard or optimal nutritional requirements for a child have been estimated by Stern,¹⁵ who found that the following quantities were consistent with normal health and growth:

Protein	2 to 3 Gm. per Kg. of body weight a day
Fat	2 to 3 Gm. per Kg. of body weight a day
Carbohydrate	6 to 10 Gm. per Kg. of body weight a day

Calculations should be made on the basis of the "ideal" or average weight for the height and age rather than for the actual weight. Several tables are available for reference.¹⁶

If we had used these figures to compute a diet for G. D. (Case I) when she was first admitted to the hospital, our prescription would have called for 80 Gm. of protein, 80 Gm. of fat, and 240 Gm. of carbohydrate. When we compare this diet with the one prescribed in 1934 for this patient (45 Gm. of protein, 53 Gm. of fat, and 110 Gm. of carbohydrate), we find that the present diet is more liberal. This difference is in accord with the change in diet prescriptions which has taken place during this period.¹⁷ The plea for more liberal diets was initiated by Sansum and others in 1926.¹⁸ Physicians were reluctant to change from the diets high in fat and low in carbohydrate which were aimed at undernutrition, and which formed the basis of the treatment of diabetes before the advent of insulin. In the last ten years carbohydrate allowances have been gradually increased until the pendulum has swung in the other direction and some authors now recommend the so-called "free diet."¹⁹ We do not subscribe to the use of the "free diet" since it introduces another variable into an already diffi-

cult problem. We also deprecate the use of diets aimed at undernutrition or to undue restriction of the carbohydrate allowance in the treatment of juvenile diabetes.

The "high carbohydrate diet," which may arbitrarily be defined as a diet containing more than 200 Gm. of carbohydrate *per diem*, has the following advantages:

1. It is less expensive.
2. It is more palatable.
3. It approximates the average American diet so that all the members of the family may partake of it.
4. There is less temptation for the child to indulge in forbidden food. "Diabetic children cannot be expected to adhere to inadequate diets."²⁰
5. The more nearly normal diet has a beneficial psychologic effect on the child.
6. Hypoglycemia is less frequent.
7. The liberal allowance of carbohydrate with the high antiketogenic factors decreases the incidence of ketosis.
8. There is a greater efficiency in the utilization of insulin.^{20, 21}
9. Hypercholesterolemia occurs less frequently.²²

Menus, calculated from the diet prescription, contain foods which are easily available and palatable. This calculation is usually done by the dietitian, but, with the help of standard tables for food values¹⁶ and a little simple arithmetic, the menu may be constructed by the physician. The patients are taught to do this before they leave the hospital. The foods selected should contain an adequate supply of the vitamins and essential minerals.

The number of meals and the proportion of the daily diet allowed at each meal are specified in each diet prescription. This last aspect of the dietary is important. In the absence of complications the meals should correspond with the family's meal hours. The diet is divided so that one fifth of the total is allowed for breakfast with two fifths for lunch and two fifths for dinner. If "buffer meals" are required, 30 Gm. of carbohydrate are taken out of the total diet and given, 10 Gm. in the middle of the morning, 10 Gm. in the middle of the afternoon and 10 Gm. at bedtime. During the course of an intercurrent acute or chronic infection or complications requiring

surgical treatment, the diet is divided into equal feedings, which are equally spaced throughout the twenty-four hours at four- or six-hour intervals.

This method, "the equal division and distribution of the diet and insulin," suggested by Duncan, Fetter, and Durkin^{23, 24} for the treatment of these complications in adult diabetic patients, has proved to be of value in the treatment of children.

Insulin.—All authorities agree that children suffering from diabetes require insulin, and preferably continuously from the day the diagnosis is made.^{2, 3, 4, 5, 7, 14}

In the presence of acute complications we employ the quick-acting unmodified insulin or zinc insulin crystals in solution.* This is used in conjunction with the equal division and distribution of the diet. When the complication is corrected and the diabetes is controlled, the diet is changed to regular meals and the slow-acting protamine zinc insulin is used to replace the unmodified insulin in whole or in part. The transfer from four injections of unmodified insulin with four equal meals to one injection of protamine zinc insulin or to a combination of protamine zinc insulin and unmodified insulin is carried out in the following manner:

The total daily dose of unmodified insulin needed to control the diabetes is divided by five, and three fifths† is given as protamine zinc insulin in the morning before breakfast. The remaining two fifths are now divided into thirds, and two thirds of the two fifths are given as unmodified insulin with the morning dose of protamine zinc insulin, the remaining third is given as unmodified insulin before the evening meal. This is a very rough guide and further adjustments are almost always necessary. The evening dose of unmodified insulin is usually dispensed with after a few days by gradually reducing the dose and adding it to the morning injection in the form of protamine zinc insulin. Most children require both the un-

* The action of zinc insulin crystals in solution (crystalline insulin) corresponds so closely to the action of unmodified insulin that they may be used interchangeably.²⁵

† If three fifths of the total dose of unmodified insulin is more than 40 units, it is safer to employ two fifths instead of three fifths with one third of the remainder as unmodified insulin in the morning and another third at night. The dosage is then modified depending on the result of the tests.

modified and the protamine zinc insulin, which are given as separate injections before breakfast.^{26, 27}

Exercise.—Juvenile diabetic patients are encouraged to take normal exercises and to enter into all the usual activities of life. This not only improves their general health and psychologic adjustment to their disease, but tends to lower their requirements for insulin. Hypoglycemia is the only danger associated with exercise if the diabetes is controlled, and the risk is proportional to the severity and duration of the exercise. Hypoglycemia can be avoided by decreasing the dose of insulin before unusual exercise or by adding extra carbohydrate. This slight inconvenience to the patient is far outweighed by the benefits derived from allowing the child to indulge in the normal activities of childhood. Every effort is made to prevent the diabetic child from developing a feeling of inferiority.

Education.—The treatment of the disease is relatively simple, but the treatment of the child may be exceedingly difficult. If this difficulty is to be surmounted, the child must be educated to live happily with his diabetes. Two weeks or more in the hospital are required to carry out the initial adjustment for a child. During this period the child receives a basic education concerning the disease and, at subsequent visits, the instruction is continued. The child and the parents are instructed in the preparation of the diet, weighing, substitutions, and the changes necessary for increased exercise or periods of mild illness when the child is confined to bed. Children over ten years of age are taught to take their insulin under the supervision of the parent or nurse. They are taught the simple tests of the urine, the test for glucose, acetone, and diacetic acid. They are also taught to recognize the symptoms of hypoglycemia so that severe reactions may be avoided.

COMPLICATIONS

The complications of juvenile diabetes may be conveniently divided into:

1. The acute or direct complications:
 - (a) Hypoglycemia
 - (b) Coma
2. The chronic or indirect complications:
 - (a) Lowered resistance to infection

- (b) Pseudo dwarfism
- (c) Premature arteriosclerosis
- (d) Juvenile cataract
- (e) Metabolic disturbances of the skin—
 1. Xanthoma diabeticorum
 2. Necrobiosis lipoidica diabetica
 3. Xanthosis
- (f) Hepatomegaly
- (g) Dental caries and pyorrhea

Hypoglycemia.—Hypoglycemic reactions occur when the blood sugar level falls too low or when the fall is too rapid. When protamine zinc insulin is used the fall in the blood sugar level is slow and a lower level is reached before symptoms appear. The most common time for "protamine reactions" is in the early hours of the morning. The severity of the reactions at this time are due to the fact that the patient, during sleep, has failed to recognize the warning symptoms and also because it is the longest period without food.

The symptoms of hypoglycemia vary greatly but are usually fairly constant for the individual patient. Some of the usual symptoms which have been noted are:

1. Dull intractable headache
2. Gnawing epigastric pain²⁸
3. Listlessness
4. Excitability or unruliness
5. Character or personality changes ("The quiet child or the child in tantrums"²⁹)

Hypoglycemic reactions are promptly corrected by giving carbohydrate by mouth if the patient is conscious and by vein if unconscious. Fifty per cent dextrose is the solution of choice for intravenous administration and 20 cc. of the solution is usually adequate. This replaces the needed carbohydrate quickly and tends to combat the cerebral edema which may occur in severe hypoglycemic reactions.

Coma.—This dreaded complication is still the most common cause of death in children suffering from diabetes.⁷ Fortunately it occurs less frequently since the advent of protamine zinc insulin and the introduction of more liberal diets.

The treatment of coma in the child, as in the adult, is aimed at the correction of the ketosis in as expedient a manner

as possible. The insulin is given early and in repeated doses. The amount depends upon the size and age of the child, the severity of the coma, and the duration of diabetes. Protamine insulin has been used successfully in the treatment of coma, but at the present time, particularly in the treatment of coma in children, it is safer to rely upon the quick-acting unmodified insulin.

A safe rule to follow in the treatment of coma is to keep the blood sugar level above 200 mg. per 100 cc. and the urine orange-colored to Benedict's test until the plasma alkali reserve is above 40 volumes per cent or the urine and plasma are free of ketone bodies. If the insulin is given too rapidly without sufficient dextrose, the child may become hypoglycemic before the ketosis is corrected.

The intravenous administration of fluids to children may present a difficult problem. Several methods of administration have been devised.^{30, 31, 32} The apparatus which we employ has proved satisfactory for this purpose.³³

Most children respond promptly to treatment with insulin, fluids, gastric lavage, salt and dextrose, but in the presence of a depressed renal function, administration of buffered sodium lactate (Hartman's solution) may be a valuable adjunct.³⁴ The mortality from diabetic coma for children treated in the hospital is almost zero.¹⁴ The mortality is distinctly greater for each succeeding decade.³⁵

Infections.—For some reason not yet understood there is a lowered resistance to infection in diabetes mellitus. Many attempts have been made to determine the nature of this lowered resistance but no satisfactory explanation has been found.³⁶ Suffice it to say that a lowered resistance to infection exists in these patients and even the most trivial infection has a profound effect on the severity of the diabetes. Almost any degree of abnormal health in the juvenile patient must be considered an emergency because slight deviations from the normal may precipitate acidosis and coma even in a patient whose diabetes has been well controlled. In the presence of a mild infection this change may take place in from twelve to twenty-four hours. For this reason the children and their parents are instructed to notify their family doctor or to report to the clinic immediately in case of illness.

The incidence of tuberculosis is higher in children suffering from diabetes than it is in the general population and is frequently seen in patients who have been in diabetic coma.^{1, 7, 37} Himsworth³⁸ concluded, however, that if the diabetes is properly controlled, these patients are no more liable to develop pulmonary tuberculosis than nondiabetic subjects.

If the child is running a fever, the equal division and distribution of the diet and insulin is employed to control the diabetes until the temperature returns to normal.

Pseudo Dwarfism.—This infrequent complication of juvenile diabetes has an insidious onset. It was first thought to be due to undernutrition, and that the only treatment necessary was an adequate diet.² Since the work of Houssay,³⁹ Long,^{40, 41} Lukens,⁴⁰ Young⁴² and others, the relationship between juvenile diabetes and abnormalities of the anterior lobe of the hypophysis has been more closely investigated. It is now believed that dwarfism associated with diabetes mellitus results from a functional hypoactivity of the hypophysis, with a lack of the growth hormone, and that undernutrition plays a secondary part.

Dwarfism does not precede the onset of diabetes. White⁵ has data, obtained within the first year of the onset in thirty-six cases, and these indicate that the patients were typical, tall diabetic children. "Dwarfism was not recognized as a rule until the fifth year of diabetes." At the onset of diabetes the child is on the average 2 inches above the standard height for the age. These children grow a little, so that retarded growth is not evident before the fifth year. This will serve to emphasize the importance of checking the annual rates of growth as well as the deviations from the standards.

Treatment comprises an abundant diet and careful control of the diabetes. One of the extraction products of the anterior pituitary gland which contains large amounts of growth hormone should be given. The administration of "growth hormone" (Antuitrin G) has been followed by increased growth in those patients treated before the closure of the epiphyses was complete.^{5, 7}

The following case will illustrate this complication of juvenile diabetes:

Case II.—C. J., a white male, aged twenty-four years, was first seen by us in 1937 when he was admitted to the hospital because of impending coma. He developed diabetes in 1923 when he was nine years of age. At the time of the onset he was a well-developed child and for the first two years his diabetes remained well controlled. A restricted diet was prescribed and he received a small dose of insulin. In 1925 he was admitted to another hospital in diabetic acidosis. Two years later (1927) he was readmitted to the same hospital in a profound hypoglycemic reaction. He continued under the care of his family doctor until 1932. During this period he suffered frequent hypoglycemic reactions. He was treated in the diabetic clinic of a second hospital from 1932 to 1937, and on one occasion was admitted for readjustment of the diet and insulin. He was subject to frequent hypoglycemic reactions, and his blood sugar level fluctuated widely from 30 to 500 mg. per 100 cc. His diet was restricted to less than 1200 calories a day during this

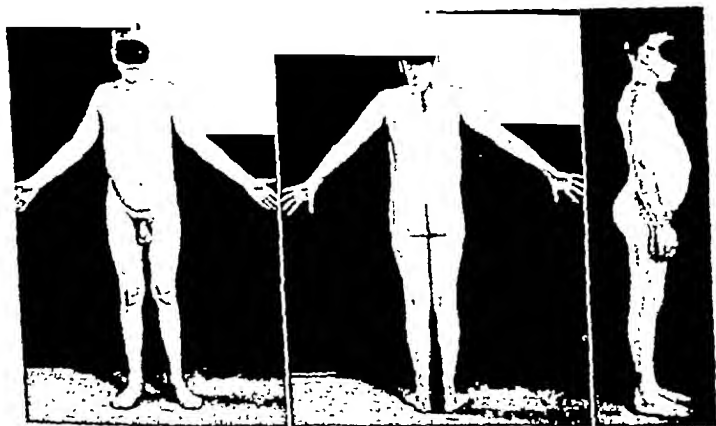


Fig. 93.—C. J. (Case II). Photograph taken in 1937, fourteen years after the onset of diabetes; age twenty-four years, weight 104 pounds (46 Kg.), and height 58 inches (147 cm.). The stature and bodily contour are illustrative of the type of dwarfism associated with diabetes mellitus.

period and he failed to gain in height after he reached the age of fourteen years.

When admitted to the hospital in 1937, he weighed 104 pounds and was 58 inches tall (Fig. 93). He was well nourished but had the appearance of a fifteen-year-old boy. His face was full and rounded; his hair was fine and silky, the eyes were normal, and there was no evidence of peripheral arteriosclerosis. A normal roentgenogram of the skull and sella turcica was obtained. Similar studies of the skeleton showed the epiphyses of the long bones to be closed. The basal metabolic rate was plus 13 per cent. Desiccated thyroid gland and whole pituitary substance had been administered before that time, but in view of the roentgenographic evidence of closed epiphyses this form of therapy was discontinued.

At present (1939) this patient weighs 111 pounds (50 Kg.) and measures 58 inches (147.5 cm.) in height. His diabetes is well controlled. The diet

contains 175 Gm. of carbohydrate, 80 Gm. of protein, and 86 Gm. of fat (1800 calories). He is taking 20 units of protamine zinc insulin and 22 units of unmodified insulin every morning.

The history of this boy's illness and the physical characteristics which he portrays are typical of the type of dwarfism associated with diabetes. It may also be observed that this type of dwarfism resembles pituitary infantilism (Fig. 93).

Premature Arteriosclerosis, Juvenile Cataract, Xanthoma Diabeticorum and Necrobiosis Lipoidica Diabetica.—These are all unusual complications of diabetes in children and fortunately are becoming more infrequent with the better control of diabetes resulting from the use of protamine zinc insulin and diets containing moderate amounts of carbohydrate and low in fat.

It is now believed that this group of complications results from hypercholesterolemia⁷ and, for this reason, a blood cholesterol below 230 mg. per 100 cc. is included in the standards for the control of diabetes. These complications are seen in children in whom the diabetes has been inadequately controlled.

Xanthosis.—This results from the faulty utilization of carotene by diabetic children. Heymann⁴³ performed carotene tolerance tests upon normal and diabetic children and demonstrated its faulty utilization in the diabetic children. The condition may be corrected by excluding from the diet vegetables of high carotene content, notably carrots and spinach, and supplying Vitamin A in the form of cod or halibut liver oil.

Hepatomegaly.—This complication of diabetes in children has recently been investigated at the New England Deaconess Hospital.⁴⁴ Hepatomegaly is usually associated with other complications of poorly controlled diabetes and is thought to be due to gross fatty infiltration of the liver. With the better control of the diabetes which results from the use of protamine zinc insulin, this complication is frequently alleviated.⁴⁵

Dental Caries and Pyorrhea.—These conditions are infrequently found in healthy children but are commonly associated with juvenile diabetes. The presence of dental caries and pyorrhea in young children should lead the dentist to suspect the possibility of unrecognized diabetes. Treatment

consists of the control of the diabetes and adequate dental care.

SUMMARY

1. Diabetes mellitus in childhood and adolescence differs from the disease in adults in its mode of onset, severity, progression, lability, endocrine relationships, hereditary incidence, association with degenerative changes, and management.

2. The treatment must be varied to take account of these differences and should be so conducted that the child is adequately nourished. The level of the blood sugar should be maintained below 200 mg. per 100 cc., and less than 10 Gm. of glucose should be lost in the urine each day. The cholesterol content of the blood should be kept below 230 mg. per 100 cc. There should be a satisfactory adjustment to the disease.

3. Liberal diets and the use of protamine zinc insulin in conjunction with unmodified insulin have greatly improved the treatment of juvenile diabetes.

4. The complications of diabetes in childhood are numerous, but with improved treatment they are less frequently seen.

5. Two cases of juvenile diabetes are reported: The first illustrates the important differences between juvenile and adult diabetes; the second, diabetic dwarfism.

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CLINIC OF DRS. GARFIELD G. DUNCAN AND
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PENNSYLVANIA HOSPITAL

THE MANAGEMENT OF THE ACUTE COMPLICATIONS
OF DIABETES MELLITUS

THERE are few greater emergencies in the practice of medicine than the acute complications of diabetes mellitus. Three problems confront the physician: first, the change in the character of the diabetes as a result of the complication; second, the management of the complication, and third, the proper evaluation of and the institution of appropriate measures to combat the influence which the diabetes has upon the complication, and *vice versa*.

A fatalistic attitude still exists toward diabetic patients suffering from acute complications. This attitude must be destroyed before these patients will receive adequate treatment. It is difficult to instill optimism where pessimism has ruled for centuries. The younger physicians and surgeons have a more effective equipment than their older colleagues had for the management of these patients, hence their approach is more courageous. This does not mean that conservative judgment is no longer necessary, but it does mean that diabetic patients now, more than ever before, are being given the same opportunities to recover from acute illnesses that patients without this disease have enjoyed. It cannot be too strongly emphasized that with the diabetes properly controlled there need be no fear to carry out any procedure which would be indicated if the patient did not suffer from diabetes. It is true that arteriosclerotic heart disease is prevalent in the older diabetic patients and that this increases the risk of surgical intervention. This increased risk has been exaggerated and it is no excuse for allowing a patient to be deprived

of necessary surgical intervention merely because he has diabetes.

All diabetic patients sooner or later are subjected to one or another acute complication. These may be classified in general terms as follows: (1) infections; (2) acute complications arising as a result of degenerative changes; of these, gangrene of the extremities and occlusion of the coronary arteries are frequently encountered; (3) conditions requiring surgical intervention; (4) ketosis; and (5) pregnancy. These complications are the common causes of death of diabetic patients. Their occurrence may be quite independent of the diabetes, such as an acute appendicitis, or their origin may be more directly related to the diabetes, as in the case of gangrene or carbuncle. In consequence of this relationship the latter are largely preventable by the proper control of the uncomplicated diabetes.

It is our purpose, in this clinic, to deal with three of the most common acute complications of diabetes in the order of their frequency. These are *acute infections*, *conditions requiring surgical intervention*, and *ketosis*. These will be dealt with individually, though it is obvious that all three may occur simultaneously in the one person. A patient seen recently illustrates this frequent combination of complications. He suffered from an acute appendicitis and became ketotic as a result of the infection.

ACUTE INFECTIONS

It is well known that an acute infection in a diabetic subject precipitates a hyperglycemia and ketosis, which may progress rapidly to coma. The action of insulin becomes impaired and under these conditions very large doses are often required to control the diabetes.

Why infection makes the diabetes more severe is not, as yet, clearly understood. Probably a number of factors are involved. Weiland (1913) and Gieger (1925) observed that fasting non-diabetic subjects developed hyperglycemia during the period of rising temperature in febrile conditions. This hyperglycemia disappeared when the temperature returned to normal. Williams and Dick (1932) found that glycosuria oc-

curring in 41 per cent of normal individuals during the course of acute infections, and Schmidt, Earland and Burns (1934) have demonstrated a temporarily impaired glucose tolerance in non-diabetic patients suffering from pyogenic infections. The effect of infection on the level of the blood sugar is not, therefore, a peculiarity confined to diabetic subjects but tends to occur in normal individuals to a milder degree. A hitherto "latent diabetes" will often manifest itself as a moderately severe diabetes during the course of an acute or chronic infection. The enormous doses of insulin which may be required by a diabetic patient with a severe infection seem to deprecate the suggestion of a mere suppression of endogenous insulin production, particularly since it can be shown that the action of this injected insulin is less effective in controlling the blood sugar level than would usually be the case. For this reason it is believed by some workers that insulin antagonists are produced which counteract the normal action of insulin. Karelitz, Cohen and Leader (1930), for example, showed that the action of insulin injected into rabbits was inhibited if it was previously mixed with the blood of diabetic patients. Control experiments in which the insulin was mixed with the blood of non-diabetic patients also showed some inhibition of the insulin action, but to a lesser degree. Some workers consider that hormones antagonistic to insulin, probably elaborated from the thyroid, anterior pituitary, or suprarenal glands, are produced in excess. Others consider that a co-enzyme of insulin fails to be produced, or that some new enzyme is produced in the serum of patients with infections and that this "antihormone" actively opposes the action of insulin. The increase in the total metabolism of the patient is a factor and alterations in the acid-base equilibrium may play a part in some cases.

Whatever the theoretical basis of the phenomenon may be the practical issue is plain and of extreme importance. Hyperglycemia and glycosuria develop as a result of the infection and the additional insulin given is less effective than it otherwise would be. Hence, it is essential to continue increasing the amount of insulin until it is adequate to control the hyperglycemia and glycosuria and to prevent the risk of ketosis and coma.

The elderly and obese patient suffering from mild diabetes, which under ordinary conditions is satisfactorily controlled by a diet without insulin, will almost always require insulin if an infection is contracted.

These patients should be given insulin during the course of acute infections and febrile disturbances if the fasting blood sugar level exceeds 120 mg. per 100 cc., or if the *post cibum* value exceeds 160 mg. per 100 cc. If the infection is a mild one and the patient is already taking insulin, a simple addition to the usual doses of insulin over the course of a few days may be all that is required to control the glycosuria and the level of the blood sugar. In more severe infections, however, other measures are indicated.

Unmodified insulin or zinc insulin crystals in solution are the preparations of choice in the presence of an acute infection. Their action is more prompt and shorter in duration than that of protamine zinc insulin. This makes them simpler weapons to manipulate when both the blood sugar level and insulin requirement may be subject to rapid alterations.

The following *method of distributing the insulin* has been employed at the Pennsylvania Hospital for the past five years with favorable results: During the course of moderately severe infections the insulin is given in four equal doses which are given at evenly spaced intervals. Thus a patient receiving 60 units of either unmodified insulin or zinc insulin crystals in solution would receive 15 units every six hours. The diet is similarly divided so that the patient receives the same amount of carbohydrate, fat and protein after each injection of insulin. It is convenient to give meals and insulin at 6 A.M., 12 noon, 6 P.M. and 12 midnight. In more severe infections the division is made into six parts, in which case the patient would receive at the outset 10 units of insulin with a sixth of the total diet every four hours. This program permits the uniform control of the blood sugar level during the most severe complications. Changes in the dosage of insulin are regulated according to the amount of sugar found in the urine, which is collected before each nourishment, and by the level of the blood sugar.

When meals and insulin are given at four-hour intervals, four-hour fractional urine collections are made, and likewise

when meals and insulin are given every six hours, the urine is collected during each six-hour period. The bladder is emptied before each feeding and the quantity of reducing substance in the urine is determined. An estimation of the blood sugar level at the same time is helpful and often necessary. During critical periods determinations of the blood sugar level are made at 8 A.M. and 4 P.M. daily. While the urine contains sugar and the blood sugar level is unduly high, the amount of insulin given is steadily increased at each administration. The diabetic patient, when recovering from the more severe type of infection, changes from six feedings at four-hour intervals with six injections of insulin to four at six-hour intervals. As the infection subsides, guided by the freedom from glycosuria and the tendency of the blood sugar level to remain low, the insulin is reduced. An added advantage of the equal division and distribution of the diet and insulin is that one determination of the blood sugar level during the day is, theoretically speaking, as good as four or six. In practice there are naturally some variations, but on the whole these are small.

Great reductions in the dosage of insulin are likely to be needed after the termination of an infection. This is especially true if the termination is rapid as in the crisis of pneumonia, the drainage of an abscess, or the amputation of a secondarily infected, gangrenous extremity. It is dangerous, however, to omit a dose of insulin during the course of an infection just because a low blood sugar value is obtained. It is remarkable with what speed hyperglycemia returns. A reduction of the amount of insulin given rather than the omission of a dose is advisable.

When the infection has subsided and the blood sugar remains at a more or less constant level it is possible to revert to the usual three meals a day with two or three doses of insulin. Finally, if insulin is necessary in health, a single morning dose of the protamine zinc insulin, with or without unmodified insulin or zinc insulin crystals in solution, may replace the more frequent injections of insulin.

Infections involving the urinary tract may invalidate glycosuria as a guide to the degree of hyperglycemia. The urinary infection may of itself lead to a disappearance or diminution of the sugar in the urine, although the blood sugar remains

TABLE 1

LIQUID DIET (SIX EQUAL FEEDINGS)

	Gm.	Protein.	Fat.	Carbohy- drate.
8 A.M.				
{ Skimmed milk	180	5.3		9
{ Cereal gruel (dry wt.)	20	3		16
Butter	6		5	
Orange juice	140			17
		8.3	5	42
12 N.				
Grape juice	160			29
{ Skimmed milk	240	7		12.5
{ 20% cream	30	1	6	1
		8	6	42.5
4 P.M.				
Ginger ale	100			16
Pineapple juice	100			12
{ Skimmed milk	240	7		12.5
{ 20% cream	30	1	6	1
		8	6	41.5
8 P.M.				
Skimmed milk	100	3		5
20% cream	30	1	6	1
{ Orange juice	200			24
{ Egg white	35	4		
{ Glucose	12			12
		8	6	42
12 M.				
Soup { Skimmed milk	240	7		12.5
{ Carrot puree	50	1.5		4.5
Butter	6		5	
Grapefruit juice	270			24
		8.5	5	41.0
4 A.M.				
Soup { Broth	120	0	0	0
{ Egg	50	7	5	
{ Gelatin	3	2.5		
Grape juice	200			36
Lactose	5			5
		9.5	5	41
Total		50.3	33.0	250.0

The division of a liquid diet containing 50 Gm. of protein, 33 Gm. of fat and 250 Gm. of carbohydrate (1500 calories) into six equal feedings is illustrated. The timing of the feedings and the constituents of the diet are also shown. This is a typical diet arrangement for diabetic patients when the diabetes is complicated by acute medical or surgical conditions.

high. Thus a diabetic patient under our care in the Pennsylvania Hospital was found to have no sugar in her urine, although the blood sugar level at the same time was 480 mg. per 100 cc. and she had not received insulin. This patient's urine was thick with pus and on culture *B. coli* and streptococci were found.

When the diabetes is complicated by an infection the *diet* requires some modification from the usual form. The protein content of the diet must be reduced in most instances of acute infection because it becomes unpalatable. Liquid nourishment may be all that the acutely ill patient can take and this should consist largely of fruit juices, skimmed milk, cream, gruels and ginger ale with glucose (Table 1). In prolonged infections, however, adequate protein, $\frac{2}{3}$ to 1 Gm. per kilogram of body weight, in an easily digestible form must be given. The daily carbohydrate intake is increased by 20 to 100 Gm. or more, and the fat is reduced to 40 to 50 Gm. a day. By this means the caloric requirements of the body are satisfied and the danger of ketosis is minimized.

A diet for a patient weighing 70 Kg. might contain protein 50 Gm. (approximately $\frac{2}{3}$ Gm. per Kg. of body weight), carbohydrate 280 Gm. (4 Gm. per Kg.) and sufficient fat, 50 Gm., to make a total of 1750 calories (25 calories per Kg.).

The following illustrative case reports are presented:

Case I.—Female, aged forty-seven years. Weight 166 pounds (75 Kg.). Height 58 inches (145 cm.). This patient was obese but was not known to have diabetes. Admitted on December 7, 1938, with a history and physical findings typical of lobar pneumonia. A "head cold" was followed by pain in the left side of her chest which kept her in bed for some days. Her temperature was 104° F.; herpes labialis were present; there were signs of consolidation of the lower lobe of the left lung and a friction rub was audible. The blood count revealed 18,800 leukocytes per cu.mm. Pneumococci, type IV, were cultured from her sputum. Examination of the urine revealed sugar and acetone bodies and the blood sugar level was 217 mg. per 100 cc.

A liquid diet containing 250 Gm. of carbohydrate, 50 Gm. of protein and 60 Gm. of fat (1740 calories) was prescribed. This diet was divided into equal meals which were given at four-hour intervals day and night (4 A.M., 8 A.M., 12 N., 4 P.M., 8 P.M. and 12 M.). As the fever subsided the feedings were reduced to five, then to four, and finally to three a day. Insulin was given in equal doses, one dose before each meal, and the urine collected before each meal was tested for sugar. The blood sugar was estimated daily for the first six days (Table 2).

TABLE 2

CASE I. SHOWING PROMPT CONTROL OF THE HYPERGLYCEMIA FOLLOWING EQUAL DIVISION AND DISTRIBUTION OF THE DIET AND INSULIN. THE INCREASING NEED FOR INSULIN AS THE INFECTION PROGRESSED AND THE REDUCED NEED WITH RECOVERY ARE EXEMPLIFIED

	Blood sugar (mg.).	Urine sugar.	Insulin (units).						Meals per 24 hours.
Dec. 8	217	Traces	10	15	10				6
9	197	"	10	10	10	10	15	15	6
10	189	"	15	15	15	15	15	15	6
11	126	Nil	15	15	15	15	15	15	6
12	142	"	15	15	15	15	15	15	6
13	121	"	15	15	15	15	15		5
16	131	"	15	15	15	15			4
19	...	"	15	15	15				3
21	93	"	12	12	12				3
23	...	"	8	8	8				3
26	...	"	5	5	5				3
28	...	"	Nil						3
30	98	"	"						3

The patient made a satisfactory recovery. A dextrose tolerance test on January 6 showed a prolonged hyperglycemia, but there was no glycosuria.

Case II.—Male, aged forty-four years. Height 58 inches (170 cm.). Weight 152 pounds (69 Kg.). Admitted on September 22, 1935, in a semi-comatose condition. He had had symptoms typical of diabetes for three months. Examination of the urine revealed acetone and diacetic acid in large quantities and an abundant glycosuria. The blood gave a positive reaction for acetone bodies (Rothera-Wishart) and contained 326 mg. of sugar per 100 cc. His temperature was normal. A continuous intravenous "drip" of 5 per cent dextrose in normal saline was begun and 40 units of unmodified insulin were given subcutaneously at six-hour intervals. He was able to take nourishment by mouth twenty-four hours after admission, when a diet containing protein 80 Gm., carbohydrate 200 Gm. and fat 75 Gm. (1800 calories) was prescribed. This was divided into four equal feedings and given at six-hour intervals with 41 units of unmodified insulin given in four doses. On September 24, the urine was free from acetone bodies and contained less sugar and his blood sugar level had decreased to 240 mg. per 100 cc.

On the following day (September 25) the patient's temperature rose to 103° F. and a reddened swollen area with evidence of lymphangitis appeared on his right arm. His blood contained 310 mg. of sugar per 100 cc. and glycosuria persisted. He received unmodified insulin, units 20-15-20-10, but in view of the severity of the infection and the febrile reaction the diet was divided into six feedings and the insulin dosage was increased and was given at four-hour intervals (Table 3). On September 26 the abscess which had developed was drained and thereafter his condition improved rapidly. His temperature returned to normal on September 28. The insulin requirement

TABLE 3

CASE II. SHOWING THE CHANGING INSULIN NEED DURING AND AFTER AN ACUTE INFECTION AND THE EASE WITH WHICH THE DIABETES WAS CONTROLLED BY THE METHOD EMPLOYED

	Blood sugar (mg.).	Urine sugar.					Insulin (units).						Meals per 24 hours.
Sept. 27	246	++++	++++	++++	++++	++++	14	14	14	14	14	14	6
28	207	++	+	0	+	++	20	20	20	20	20	20	6
29	186	0	0	0	0	0	20	20	20	20	20	20	6
30	80	0	0	0	0	0	17	17	17	17	17	17	6
Oct. 1	...	0	0	0	0	0	22	22	22	22			4
2	...	0	0	0	0	0	22	22	22	22			4
3	66	0	0	0	0	0	19	19	19	19			4
4	182	0	0	0	0	0	12	6	8	6			4
6	...	0	0	0	0	0	10	6	7	5			4
7	...	0	0	0	0	0	9	5	6	4			4

decreased steadily and, on October 4, the number of injections and meals were reduced to four a day.

Further reductions in the amount of insulin were made, three meals a day were instituted, and when the patient was discharged at the end of the month he no longer required insulin and two dextrose tolerance tests were performed, the results of which were normal. This patient was admitted two years later with uncontrolled diabetes and an active pulmonary tuberculosis which proved fatal.

Case III.—Male, aged fifty-nine years. Weight 154 pounds (70 Kg.). Carbuncle of neck. Admitted on December 24, 1934. Two weeks before admission he had noticed some soreness and a small swelling on the back of his neck. No history of diabetes nor symptoms suggestive of this disease were obtained, nor had any member of his family had diabetes. He was obese and he had on his neck a carbuncle about 4 inches in diameter with a necrotic wall. There was considerable glycosuria and his blood sugar was 354 mg. per 100 cc. His temperature was 100.4° F. and the leukocyte count was 26,000 per cu.mm.

TABLE 4

CASE III. SHOWING THE INSULIN REQUIREMENT DURING AND AFTER AN ACUTE INFECTION

Date.	Blood sugar (mg.)	Urine sugar.	Insulin (units).						Meals per 24 hours.
Dec. 24	354	++	10	10	10	10	10		6
25		+	10	10	10	10	10	10	6
26	284	trace	20	16	14	16			4
27	222	0	20	16	18	16			4
29	150	0	20	16	18	16			4
31	124	0	24	20	26				4
Jan. 8	91	0	22	18	18				3
10	109	0	22	18	18				3
12	110	0	18	16	18				3

The carbuncle was incised. A diet containing protein 70 Gm., carbohydrate 150 Gm. and fat 75 Gm. (1550 calories) was prescribed and was divided into six equal feedings and given at four-hour intervals. Ten units of insulin were given before each feeding. He received two feedings and two doses of insulin before and 200 cc. of 10 per cent glucose solution in normal saline given intravenously after, the operation. The wound healed well and there was a rapid amelioration of the diabetes (Table 4). The patient's condition improved rapidly, but he left the hospital, against advice, before it was possible to further reduce the amount of insulin.

Pulmonary tuberculosis is a common complication of diabetes mellitus. When this complication is encountered the method of controlling the diabetes is similar to that described above. The insulin requirement varies with the activity of the tuberculosis. Moreover, these variations may extend over a longer period than in the case of an acute infection. An occasional diabetic patient manifests a steadily decreasing need for insulin as the tuberculous process progresses. These patients are exceptions to the rule. Anything that tends to reduce the toxicity of the infection, whether it be rest and other general measures or certain specific procedures such as the induction of artificial pneumothorax, will tend to lessen the insulin requirement. The more prolonged nature of the infection increases the importance of prescribing a diet of adequate caloric value. To illustrate the method of treatment, the following brief case-report is included:

Case IV.—Female, aged twenty years. Weight 100 pounds (49 Kg.). Height 62 inches (155 cm.). Diabetes mellitus complicated by pulmonary tuberculosis. On admission a diet containing protein 80 Gm., carbohydrate 250 Gm., and fat 75 Gm. (2000 calories) *per diem* was prescribed. This was given in four equal meals at six-hour intervals. Thirty units of unmodified insulin were given before each meal. After three weeks the insulin dosage was gradually reduced to four doses of 16 units each. At this time the fasting blood sugar level had fallen to 59 mg. per 100 cc. Three days later, when her insulin was reduced to four doses of 12 units each, it was found that the blood sugar level, taken at the same hour as before, had risen to 212 mg. and that the urine contained sugar and ketone bodies. The amount of insulin was increased and the hyperglycemia was controlled.

Summary.—The foregoing cases illustrate: (1) patients who have discernible diabetes only during the course of acute infections, (2) the increasing insulin requirement while the infection is progressing unfavorably and the decreasing need as the infection subsides, and (3) the ease with which the

diabetes is controlled during acute infections by using unmodified insulin and the equal division and distribution plan, affecting both the diet and the insulin. This method has been employed for more than 200 patients suffering from acute complications of diabetes at the Pennsylvania and Jefferson Hospitals with satisfactory results.

COMPLICATIONS OF DIABETES MELLITUS WHICH REQUIRE SURGICAL TREATMENT

Diabetic patients are susceptible to certain conditions requiring surgical intervention, *e.g.*, *gangrene*, *carbuncles*, *abscesses* and *cellulitis*. Poor treatment or no treatment for the diabetes increases remarkably the likelihood of these complications. Such patients are prone to develop arteriosclerotic changes obstructing and reducing the circulation. These changes are especially noticeable in the legs and feet, though any part of the body may be affected.

The exact causes of these changes are not known. High fat and high cholesterol contents in the blood are believed, by Rabinowitz⁶ and others, to predispose to arteriosclerosis. Diets having high fat and low carbohydrate contents predispose to high blood fat and cholesterol values. Fortunately the present trend of treatment is to give less fat and more carbohydrate in the management of diabetes. This regimen tends to reduce the fat and cholesterol concentrations in the blood. Others, notably Allen,^{7, 8} believe that a prolonged hyperglycemia is an important predisposing cause of the arterial changes in these patients. If this is true, a uniform control of the diabetes will aid in preventing gangrene.

We believe that this is so. Accordingly we aim to control the diabetes and at the same time employ diets which will also restore the fat and cholesterol values of the blood to normal. The amount of sugar in the blood should be below 130 mg. per 100 cc. (fasting) and should not exceed 160 mg. per 100 cc. after meals. Unfortunately there is a prevalent tendency to consider normal fasting blood sugar values as sufficient evidence that the diabetes is under control. It is a simple matter to secure normal fasting blood sugar values with protamine zinc insulin alone, but one must not be unmindful that hyperglycemia tends to occur later in the day.

Control of the diabetes, and the use of diets containing over 130 Gm. of carbohydrate and less than 75 Gm. of fat, will reduce the incidence of degenerative changes. Thus surgical complications often may be prevented.

Gangrene.—Patients occasionally present themselves for the treatment of gangrene unaware of the cause until diabetes is recognized on routine investigation. The diabetes in these cases is usually mild until aggravated by a secondary infection, fever, or toxemia.

Innocent appearing bullae on the toes or heel frequently herald the onset of gangrene. In a day or two there is a dark discoloration of the underlying tissues and the true nature of the complication becomes obvious. There may be a history of trauma. A minor injury, whether from a blow, the paring of corns, the cutting of toe nails, poorly fitting shoes, infection, exposure to extremes of temperature, or to irritating chemicals, is sufficient to precipitate gangrene. Gangrene occurs, for the most part, in patients over forty years of age with mild, long-standing neglected diabetes, and males are more frequently affected than females.

Of the several methods of determining the state of the circulation in a limb by far the most important are inspection and palpation. A foot which when held for several minutes in a dependent position retains its normal color has a good circulation. The foot which promptly develops a reddish cyanosis when placed in a dependent position and which pales rapidly on elevation has a poor circulation. When the toes and heel are warm there is at least a fairly good circulation, whereas a cold foot suggests extensive vascular disease, especially if there is also pain in the leg muscles on exercise.

A palpable pulsating dorsalis pedis and posterior tibial artery may be reassuring. It is not uncommon, however, to see a patient whose feet are cold and yet who has an easily demonstrable dorsalis pedis artery pulsation. On the other hand, Mrs. C. C. (Case 5), whose case is presented below, had no dorsalis pedis or posterior tibial pulsation and yet an excellent collateral circulation accounted for a normal warmth in the foot. If we had to choose between a good dorsalis pedis pulsation with a cold foot and an absent pulsation with a warm foot, we should choose the latter. The temperature of the foot

is the most important single guide in assaying the efficiency of the local circulation.

Roentgen examination to determine the degree and extent of calcification of the arteries sometimes aids in deciding the site of amputation. The histamine test is also of some value, but like the oscillometer readings adds little to what can be observed by sight and touch.

Routine investigation of the circulation of the legs and feet in all diabetic patients over thirty-five years of age discloses all degrees of impaired circulation. These examinations make it possible to select those patients who will be benefited by foot exercises. Buerger's*⁹ exercises are excellent and are of value in preventing or postponing the onset of gangrene. They should not be employed in the presence of gangrene and secondary infections.

The main *indications for surgery* when gangrene is present are: (1) a rapidly extending gangrene and spreading infection with *no tendency to localize*; (2) extensive osteomyelitis; the amputation of a toe may be successful if osteomyelitis has not involved the metatarsal bones, but if the metatarsals are involved, local amputation is seldom successful; and (3) intractable pain and evidences of advanced vascular disease.

Illustrations of the management of diabetic patients requiring surgery are presented below:

Case V.—Female, aged sixty-eight years. Weight 137 pounds (62 Kg.). Height 62 inches (155 cm.). Arteriosclerotic heart disease with mild cardiac decompensation; diabetes mellitus; bilateral cataract; and gangrene of two toes with osteomyelitis of metatarsal and phalangeal bones.

This patient was admitted to the Pennsylvania Hospital under the care of Dr. W. E. Lee on December 27, 1938. Her family history was irrelevant and the only past illness of significance was a carbuncle in 1937. She had had diabetes for at least four years.

There was an infection about a callus on the plantar surface of the left foot, with a triangular area of discoloration, a mixture of inflammatory reaction and cyanosis, and marked tenderness and fluctuation over the metatarsophalangeal area. The dorsum of the foot was swollen, hot and tender. There was no palpable pulsation of either the posterior tibial or dorsalis pedis artery, but the tips of the toes and the heel were warm and the histamine

* Buerger's exercises consist of blanching the foot by elevation (usually requiring one half to three minutes), then producing a reactionary hyperemia by placing the foot in a dependent position for one to two minutes, and then resting the leg on bed in horizontal position. Six such cycles may be carried out three or four times daily.

flare tests gave evidence of good circulation down to the ankle. On roentgen examination, the arteries of the foot were plainly visualized and there was destruction of the second metatarsophalangeal joint, the base of the proximal phalanx, and the head of the metatarsal bone.

Amputation of the foot was decided upon. In spite of the absence of palpable pulsation of the large arteries the warmth of the foot and toes indicated a good collateral circulation and a low amputation was considered safe.

The insulin requirement had increased to 80 units daily. The insulin and meals were given at six-hour intervals because of the infection and the accom-

TABLE 5

CASE V. SHOWING THE PRE- AND POSTOPERATIVE TREATMENT OF A DIABETIC PATIENT WITH GANGRENE

Date.	Diet.				Insulin, units.		Blood sugar, mg.	Urine sugar.	Remarks.
	P.	F.	C.	Cal.	Distribution.	Total.			
1939	Gm.								
Jan. 13	70	65	160	1500	20-20-20-20	80	80	0 0 0 0	4 meals.
16	70	65	160	1500	20-20-20-20	80	...	0 0 0 0	
17 8 A.M.	203	4+	No break-fast.
9 A.M.	500 cc. dextrose solution (5%) in normal saline.								
10 A.M.	Operation.				Foot amputated.
Midday	17	16	40	375	20	Liquid diet.
4 P.M.	17	16	40	375	20	...	200	
10 P.M.	17	16	40	375	20	60			
18	70	65	160	1500	22-25-25-25	97	216 (8 A.M.)	2+2+3+0	Soft diet.
19	70	65	160	1500	25-25-25-25	100	105	0 0 0 0	Regular diet.
20	70	65	160	1500	25-25-25-25	100	82	0 0 0 0	
21	70	65	160	1500	25-25-25-25	100	144	0 0 0 0	
22	70	65	160	1500	20-20-20-20	80	160	0 0 0 0	
23	70	65	160	1500	*(30)-0-0-0	60	0 0 0 0	3 meals.
25	70	65	160	1500	(30)-0-0-0	60	176	0 0 0 0	
30	70	65	160	1500	(40)-0-0-0	40	113	0 0 0 0	
Feb. 2	70	65	160	1500	(30)-0-0-0	30	77	0 0 0 0	

* Protamine zinc insulin in parentheses.

panying fever. Ordinarily, on the day of operation a liquid breakfast is given at 6 A.M., preceded by the usual amount of insulin. In this case, through a misunderstanding, the breakfast and early morning insulin were omitted.

On the morning of the operation (January 17), 500 cc. of a 5 per cent solution of dextrose were given intravenously. At 10 A.M., under spinal anesthesia, the left foot was amputated just above the ankle. At noon of the same day, the patient was able to take her regular feeding and on the following day, she was up in a wheel chair. The details concerning the diet and insulin, and the blood and urine analyses are presented in Table 5.

The patient made an uneventful recovery.

Case VI.—Female, aged forty-three years. Admitted to the Jefferson Hospital under the care of Dr. T. Shallow on February 19, 1938. She complained of abdominal pain which was generalized at first (February 17); later the same day the pain became localized in the right lower quadrant. She had no desire for food.

This patient had been attending the diabetic clinic since January, 1938. She had a mild diabetes and did not require insulin.

Abdominal pain had been complained of "off and on" since April, 1937, but this was attributed to a "cyst." On February 17, 1938, the pain was sudden, sharp and caused her to "double up." In an attempt to obtain relief a dose of magnesium sulfate was taken. This was effective but the pain did not abate. The patient attended the diabetic clinic on February 19 and was admitted to the hospital. She was extremely ill. Her temperature was 100° F., pulse rate 142 and respirations 36 per minute. The blood pressure was 190 mm. Hg systolic and 128 mm. diastolic. There was considerable sclerosis of the peripheral arteries and she was moderately obese. The skin was dry and hot, the tongue and pharynx dry and red, the heart sounds distant, and the abdomen was obese. The muscles of the right side of the abdomen were spastic with marked tenderness over the entire right lower quadrant.

The urine contained 1.4 per cent of sugar and acetone was present. The CO₂ combining power of the blood plasma was 37.5 volumes per cent and the blood sugar (fasting) level was 220 mg. per 100 cc.

The diagnoses were: acute suppurative appendicitis with localized peritonitis; diabetes mellitus; ketosis; generalized arteriosclerosis with arterial hypertension, and obesity.

An immediate operation was advised. One liter of 5 per cent dextrose solution in normal saline was given intravenously and 25 units of unmodified insulin were injected subcutaneously. The patient was given morphine sulfate, gr. 1/4, and atropine sulfate, gr. 1/160, at 3:15 P.M. and spinal anesthesia was given at 4:30 P.M.

A perforated appendix and a localized accumulation of pus was found in the appendiceal region. The appendix was removed and two drains were left in place.

Immediately after the operation 1000 cc. of 10 per cent dextrose in normal saline were given slowly by venoclysis and 20 units of unmodified insulin were given subcutaneously (Table 6).

The plasma sugar content at 8:30 P.M. was 200 mg., and the CO₂ combining power of the blood plasma was 37.5 volumes per cent. A 10 per cent solution of dextrose was given slowly but continuously. Every third liter of dextrose solution was given in normal saline. The insulin was increased until, on February 21, a satisfactory blood sugar level was obtained (159 mg. per 100 cc.) and the CO₂ combining power of the blood plasma was 67.2 volumes per cent.

The abdomen had become soft by February 22, though there was continuous fever. Neither food nor liquids had been allowed by mouth. Nutrition was maintained by the slow, continuous, intravenous administration of 10 per cent dextrose. On February 25, fluids were allowed by mouth and a diet (liquid) containing 60 Gm. of protein, 200 Gm. of carbohydrate and 51 Gm. of fat (1500 calories) was begun.

There was a gradually diminishing purulent discharge from the incision until March 18. The infecting organism was the *Staphylococcus aureus*.

TABLE 6

CASE VI. SHOWING THE DETAILS OF TREATMENT AND THE LABORATORY DATA IN A CASE OF DIABETES COMPLICATED BY ARTERIO-SCLEROSIS AND A LOCALIZED PERITONITIS FOLLOWING A RUPTURED APPENDIX

Date.	Diet.			Insulin.		Blood.			Urine.		Fluids.		Remarks.
	P. Gm.	F. Gm.	Total cal.	Units per injection.	Total number of units.	Sugar in mg. per 100 cc.	CO ₂ vol. %.	Sugar, %.	Acetone.	Intake in cc. 24 hrs.	Output in cc. 24 hrs.		
Feb. 19	Preoperative. 1000 cc. 5% glucose. Postoperative. 2000 cc. 10% glucose. 1000 cc. 10% glucose in normal saline.												
20	3000 cc. 10% glucose.			35-35	95	220* 210	37.5	1.4	+	4000	1175	*Fasting blood sugar before admission. Operation 4.30 P.M.	
21	1000 cc. 10% glucose in normal saline intravenously.			35-35-35-45-45	230	200 (8:30 P.M.) 222 (A.M.)	34.7	2.9	+	4000	1000	Glucose alone and with saline given slowly and continuously via indwelling venous cannula.	
22	4000 cc. 10% glucose.			45-45-40-40-40	250	236 (P.M.) 194 (A.M.)	51.9 51.9	2.5	0	5000	950		
23	1000 cc. 10% glucose in normal saline.			40-40-40-45-45	250	139 (P.M.) 215 (A.M.)	67.2 55.8			5000	1025		
24	3000 cc. 10% glucose.			45-45-45-45	225	182 (A.M.)	63.3	1.6	0	5000	1350	45 units given before each liter of glucose solution.	
25	2000 cc. 10% glucose in normal saline.			45-45-45-40	175	126 (4 P.M.) 98 (A.M.)		1.0	0	4000	1300		
26	51 200 1500			40-40-40-10	160	114 (4 P.M.)							
27	60 51 200 1500			30-30-30-30	120	141 (A.M.) 69 (P.M.)		0	0	5000	900	Diet (liquid) in 4 equal feedings 1 every 6 hours.	
28	60 51 200 1500			16-16-16-16	64	109		0	0	2000	1000	Solid food permitted.	
29	60 51 200 1500			16-16-16-16	64			0	0	2100	1000		
Mar. 3	60 51 200 1500			14-14-14-14	56			0	0	2100	1000		
8	60 51 200 1500			14-14-14-14	56			0	0	3800	800		
13	70 44 180 1400			14-14-14-14	56			0	0	3600	1075		
20	70 44 180 1400			14-14-14-14	56	98		0	0	4000	1700		
23	70 44 180 1400			(46)-0-0				0	0	3000	800	Discharged.	
	70 44 180 1400			(46)-0-0				0	0	2900	900		

†Protamino zinc insulin in parentheses.

† Protamine zinc insulin in parentheses.

Comment.—There were several important considerations in the management of this patient:

1. An overweight patient having a mild diabetes acquired an acute infection. The effect of acute infections with fever is always unfavorable in diabetic patients. The anorexia with the resulting reduction in the carbohydrate intake occurring at a time when the total metabolism is increased by fever predisposes to ketosis. The increased metabolism is carried on at the expense of the body fats, the incomplete combustion of which produces a ketosis. A vicious circle is thus established: infection and fever, loss of appetite, low carbohydrate intake, increased total metabolism, increased fat breakdown, and ketosis.

The vicious circle is broken by four measures: (1) an adequate carbohydrate intake; (2) sufficient insulin (these measures correct the disproportionately high fat metabolism); (3) the eradication of the infection (this reduces the total metabolism, dissipates the fever and restores the appetite); and (4) adequate liquids are of value in correcting and preventing dehydration. The need for insulin decreases as convalescence is established. Shortly after her discharge from the hospital this patient no longer required insulin.

We wish to emphasize again that although the diabetes was mild in this overweight patient, nevertheless the demands created by an acute infection aggravated the diabetes and emergency measures were necessary. *It is remarkable how frequently the changing status of the diabetes during acute infections is disregarded.*

2. This patient, though only forty-three years of age, had an arterial hypertension with extensive arteriosclerosis. The latter is common, especially when the diabetes is mild and has been untreated for long periods. It can be assumed that any diabetic patient at or beyond middle life presents, because of these changes, a greater surgical risk than non-diabetic subjects.

3. A point of interest was the activity of the patient in spite of the seriousness of her illness. Widespread abdominal infections in diabetic patients often cause fewer symptoms than is ordinarily found in patients not having diabetes.

4. The *preoperative treatment* of the diabetes. Was it

wise to operate so early, or should the surgeon have waited for a lower blood sugar level and a higher CO_2 combining power of the blood plasma? Major surgical procedures should be delayed if the blood sugar exceeds 300 mg. per 100 cc. with a CO_2 combining power of the plasma below 35 volumes per cent, with strong reactions for acetone bodies in the blood plasma and urine. During this delay the ketosis may be corrected by giving fluids, glucose, chlorides and insulin.

For the patient under consideration no delay was necessary. In fact, as in most cases, the most important step in the treatment was to eradicate the infection as early as possible. Hence a safe dose, 25 units, of unmodified insulin was given and partial correction of the dehydration was accomplished by the intravenous administration of 1 liter of a 5 per cent solution of dextrose in normal saline.

5. *The Anesthetic.*—Spinal or local anesthesia is suitable for diabetic patients when there are no contraindications. Vomiting is less likely after a spinal than after a general anesthetic. Nitrous oxide and oxygen anesthesia is quite satisfactory for these patients, and we do not hesitate to use ether if any special indication for it arises. The objections to it are the length of the period of anesthesia and the tendency to nausea and vomiting following its use.

Neither chloroform nor ethyl chloride should be used in diabetic patients.

6. *The Surgeon.*—Such operations are better performed by a surgeon who has an abiding interest in and realizes the special needs of the diabetic patient. He performs the operation as expeditiously as circumstances will permit and co-operates with the internist.

7. *Postoperative Management.*—The postoperative management was complicated by the contraindication to giving nourishment by mouth. Nourishment was provided by the slow but continuous administration of dextrose with sufficient insulin at four-hour intervals to maintain a satisfactory blood sugar level.

Case VII.—Female, aged twenty-seven. Weight 155 pounds (70 Kg.). Height 59 inches (147 cm.). Admitted to Dr. Clifford Lull's service at the Pennsylvania Lying-In Hospital on April 4, 1939, for the termination of a full-term pregnancy by a cesarean section. The patient was known to have had diabetes for fifteen years. Just prior to becoming pregnant she required

40 units of zinc insulin crystals in solution daily (two doses). Her insulin requirement increased, particularly during the first and third trimesters, until she was taking 130 units daily in three doses. Two weeks before term the diet was reduced gradually from 1800 to 1100 calories because of a rapid gain in weight. A reduction in the insulin given, from 130 to 88 units, ensued.

On admission her diet contained protein 60 Gm., carbohydrate 150 Gm. and fat 29 Gm. (1100 calories). She received 88 units of zinc insulin crystals in solution *per diem*.

The blood sugar (fasting) level was 155 mg. per 100 cc. There was constant glycosuria due to a proved low renal threshold for dextrose.

A roentgen examination of the pelvis revealed some contraction of the transverse diameter. The patient had developed puffiness of the face and ankles. Her blood pressure had increased over a period of one week from 150 mm. of Hg systolic and 90 mm. diastolic to 190 mm. systolic and 110 mm. diastolic and showers of granular casts were found in the urine. These evidences of toxemia and not the diabetes *per se* were the indications for the cesarean section.

On the day of operation, April 6, this patient was given a liquid breakfast containing protein 15 Gm., carbohydrate 62 Gm. and fat 5 Gm. (350 calories) at 6 A.M. preceded by 22 units of insulin (unmodified), one quarter of her usual daily requirement.

At 11 A.M., 250 cc. of a 10 per cent solution of dextrose was given intravenously and the operation was performed at 11:30 A.M., under nitrous oxide, oxygen and ether anesthesia. Unmodified insulin, 22 units, was given immediately after operation.

At 2 and 8 P.M., and at 2 A.M., 1000 cc. of a 10 per cent solution of dextrose in normal saline were given by venoclysis, each preceded by 22 units of insulin. At 8 A.M. on April 7 a diet containing protein 60 Gm., carbohydrate 250 Gm. and fat 18 Gm. (1400 calories) was prescribed. This food was given in liquid form and was divided into six equal feedings, one every four hours. Beginning on April 11 it was given in four feedings.

The insulin requirement fell rapidly after delivery to 6 units before each meal on April 11.

The mother had inadequate breast milk and, with the cessation of nursing, a gradual increase in the insulin requirement followed. At the time of discharge, on April 21, she required 28 units of zinc insulin crystals in solution before breakfast and 20 units before supper and her diet after April 18 contained 60 Gm. of protein, 175 Gm. of carbohydrate and 84 Gm. of fat (1600 calories).

On this regimen the sugar content in her blood was 112 mg. per 100 cc. on April 25.

The baby was a normal male and weighed, at birth, 6 pounds and 6 ounces. Lactose solution was given to the baby every two hours for the first three days of life.

This case illustrates two complications of diabetes: pregnancy and surgical intervention. The preoperative and postoperative management employed in this instance is the same as that used in diabetic patients not requiring emergency operations. The mother's recovery and the baby's progress have been uneventful.

SUMMARY

1. Arteriosclerosis is an important factor in predisposing to surgical complications in diabetic patients.

2. Diets containing liberal quantities of carbohydrate but small amounts of fat tend to reduce the blood fat and cholesterol values. In this manner, and with control of the diabetes, they tend to prevent arteriosclerotic changes.

3. The relative values of inspection, palpation, and roentgen and oscillometric examinations and histamine tests in evaluating the circulation in the feet of diabetic patients are discussed.

4. The management of three surgical diabetic patients is presented. The first illustrates the treatment of diabetic gangrene; the second, the management of diabetes in the presence of an acute suppurative appendicitis and localized peritonitis; and the third, cesarean section.

DIABETIC COMA (KETOSIS)

Diabetic coma, since the introduction of insulin, has been surpassed as a cause of death by diseases of the cardiovascular system and acute infections. Nevertheless every diabetic patient is a potential candidate for ketosis and, given the proper set of circumstances, ketosis will result. A relative or absolute inadequacy of insulin, decreased carbohydrate metabolism and incomplete combustion of fats provide the pathologic-physiological basis of ketosis.

Ketosis is precipitated by: (1) acute infections, (2) omission of insulin, (3) vomiting, (4) diarrhea, (5) prolonged neglect of the diabetes, and (6) indiscretions in the diet. The combination of acute infections and the omission of insulin because of the ensuing anorexia is frequent. There is no quicker way of precipitating a ketosis.

Case VIII. Impending Coma.—Male, aged nineteen years. Weight 136 pounds (62 Kg.). Height 68 inches (170 cm.). This patient was known to have had diabetes four years when admitted to Dr. Hobart Reimann's Service at the Jefferson Hospital at 12:30 P.M. on April 28, 1939. He had been well until April 24 when he contracted an acute infection of the upper respiratory tract. There was no improvement and, on April 27, he began to vomit. He vomited twenty times and because of this omitted his insulin (60 units of protamine zinc and 12 units of unmodified insulin) on April 28.

When seen at 2 P.M. on this date the following observations were made:

Marked air hunger with hiccoughs, flushed cheeks, dry skin, decreased intra-ocular pressure, tongue and pharynx red and dry, abdomen moderately distended with marked tenderness and moderate muscle rigidity, blood pressure 146 mm. Hg systolic and 75 mm. diastolic, pulse rate 98 and respirations 36 per minute. His body temperature was normal on admission, but shortly thereafter it rose to 102° F. and continued to be elevated for four days during the course of an acute tracheitis and bronchitis.

The urine contained 3 per cent of sugar and the reactions for acetone and diacetic acid were strongly positive.

The blood sugar level was 336 mg. per 100 cc. and the CO₂ combining power of the plasma was 24 volumes per cent. The leukocyte count was 14,500 per cu. mm.

The immediate treatment consisted of: (1) *Insulin*, 100 units of protamine zinc and 100 units of unmodified insulin given subcutaneously as soon as the diagnosis of diabetic ketosis was made. (2) *Carbohydrate*. One liter of a 10 per cent solution of dextrose in normal saline was given slowly by venoclysis. (3) *Chlorides*. An additional 1000 cc. of normal saline was given intravenously and, when tolerated, he was given salty broths by mouth. (4) *Additional fluids* were given freely by mouth after the vomiting and abdominal pain had subsided. (5) *Warmth* was provided by suitable coverings and hot-water bottles to the extremities. Hot liquids were given by mouth when the patient's condition warranted. (6) An enema was given early in the treatment. (7) A gastric lavage was not done. (8) *No alkalis* were given.

The CO₂ combining power of the blood plasma was determined at 1, 4 and 11 P.M. and was found to be 24, 24 and 40 volumes per cent and the level of the blood sugar was 336, 336 and 166 mg. per 100 cc., respectively. With satisfactory progress no additional insulin was given until midnight, when he was given the first nourishment by mouth. The diet contained 60 Gm. of protein, 29 Gm. of fat and 250 Gm. of carbohydrate (1500 calories) and was divided into six equal meals at four-hour intervals. Twelve units of insulin were given before each meal. Each dose was increased to 16 units on April 30 because of a hyperglycemia (227 mg. of sugar per 100 cc.). As the infection subsided the nourishments were reduced to four daily, one every six hours, and finally on May 5 three meals were resumed. The multiple doses of insulin were then replaced by a dose each of protamine zinc and unmodified insulin, both given in the morning before breakfast.

The treatment of impending coma in this instance illustrates the use of both protamine zinc and unmodified insulin. One hundred units of each were given subcutaneously at the outset of treatment.

This plan avoided the frequent administrations of unmodified insulin during the first twelve hours of treatment. At the end of this period the patient was able to take liquid nourishment by mouth. A diet containing 60 Gm. of protein, 250 Gm. of carbohydrate and 29 Gm. of fat (1500 calories) was prescribed. It was divided into six equal feedings with insulin accordingly.

Four-hour determinations of the CO₂ combining power of

the blood plasma and the blood sugar level are advisable while the patient's life is in danger. In this manner the need for additional unmodified insulin to combat ketosis and hyperglycemia, or for more carbohydrate to combat a tendency to hypoglycemia as the case may be, is recognized.

Case IX.—Male, aged thirty-one years. Weight 125 pounds (56 Kg.). Height 66 inches (165 cm.). Admitted December 23, 1937, in diabetic coma.

This patient had been admitted to the Pennsylvania Hospital on two former occasions: in August, 1935, with diabetes and a furuncle of the cheek, and in January, 1936, because of "painful feet." He was taking 77 units of unmodified insulin a day when discharged from the hospital in 1936. In January, 1937, he was admitted to the Graduate Hospital in diabetic coma and he spent April, 1937, in the Chester Hospital, when he had pneumonia. In July, 1937, he was readmitted to the Graduate Hospital in impending coma and, in December, he entered St. Agnes Hospital where the same diagnosis was made. Following his discharge on December 19 he stated that because of financial difficulties he was unable to buy food and consequently he omitted his insulin. An intense thirst and polyuria developed, followed by anorexia and nausea. For twenty-four hours before admission he was stuporous, intensely weak, and vomited "black liquid."

He was admitted (December 23) in diabetic coma. He had marked air hunger and his tissues were generally dehydrated. The skin was dry and his eyes were soft and sunken; the tongue was dry and coated and the pharynx was dry and red. The precordial dullness was increased to the left and the cardiac sounds were obscured by loud rhonchi. There was diminished expansion over the left side of the chest (later there were evidences of pulmonary atelectasis on this side). The liver was palpable three finger breadths below the costal margin. The blood pressure was 90 mm. Hg systolic and 40 mm. diastolic. The body temperature was 97° F., the pulse rate 105 per minute, and there were 28 respirations per minute.

The CO₂ combining power of the blood plasma was 8 volumes per cent and there was a 3+ reaction for plasma acetone (Rothera-Wishart test). The blood sugar level was 426 mg. per 100 cc. There was 4+ glycosuria and the urine contained large amounts of acetone and diacetic acid. There was a moderate albuminuria. Occasional hyaline casts, an occasional red blood cell and a few leukocytes were found on microscopic examination of the urine. The blood count revealed: Hbg. 90 per cent, R.B.C. 5,000,000, and W.B.C. 28,000 (polynuclear leukocytes 85 per cent, lymphocytes, 13 per cent, monocytes, 2 per cent).

The foregoing findings confirmed the diagnosis of diabetic coma and there was a complicating partial pulmonary atelectasis. Within twelve hours of the institution of treatment the body temperature increased to 102° F. and remained elevated for two days.

Treatment.—*Insulin.*—Forty units of unmodified insulin were given subcutaneously at half-hour intervals (one dose, 40 units, was given intravenously). The level of the blood sugar, the CO₂ combining power of the blood plasma and the presence of plasma acetone were determined at frequent intervals (1 P.M., 3 P.M., 4:30 P.M., 7 P.M., 9 P.M., 12 midnight, 3:30 A.M. and 7 A.M.) until a satisfactory increase in the CO₂ combining power of the blood plasma and a disappearance of the plasma acetone were accomplished. It was

CASE IX. THE TREATMENT OF A PATIENT IN DIABETIC COMA IS PRESENTED IN DETAIL, SHOWING THE AMOUNTS AND THE TIMING OF THE INSULIN ADMINISTRATION, THE CARBOHYDRATES, FLUIDS, CHLORIDES, AND THE DIET

Date.	Time.	Diet.			Insulin.	Blood.			Urine.		Remarks.
		P. Gm.	F. Gm.	C. Gm.		Sugar (mg. 100 cc.)	Acetone, Rotherm, Wihart test.	CO ₂ vol. %.	Sugar, Benedict's test.	Acetone, Rotherm test.	
Dec 23	1 P.M.					426	..	8	4+	4+	1000 cc. 5% dextrose in normal saline. Gastric lavage. B. P. 90/44.
	1:30				40	
	2:00				40 (intravenously)	
	2:30				40	422	3+	11	4+	..	
	3:00				40	
	3:30				40	
	4:00				40	423	
	4:30				40	
	5:00				40	
	5:30				40	
	6:00				40	..	3+	21	4+	4+	Normal saline 240 cc. by stomach tube. 500 cc. 2% sod. bicarb. intravenously. 1000 cc. normal saline intravenously. 325 cc. 10% dextrose intravenously. B. P. 108/54.
	6:30				40	
	7:00				40	290	3+	29	B. P. 110/60.
	7:30				40	4+	3+	
	8:00				40	
	8:30				40	
	9:00				30	416	2+	33	B. P. 100/60.
	10:00				30	
	11:00				30	
	12:00				30	316	1+	..	2+	..	1000 cc. normal saline subcutaneously.
	1 A.M.				30	
	2:30				30	
	3:00				30	374	0	..	3++	..	325 cc. 10% dextrose in normal saline intravenously. B. P. 90/40.
	3:30				30	
	4:00				30	
	5:30				30	
	6:30				30	160	0	0	
	7:00				0	0	
	8:30				..	133	0	39	0	0	B. P. 80/44.
	9:00				..	119	..	53	0	0	6 equal feedings begun (liquid) at noon.
	12:00				30-30-30	1600	0	0	4 equal feedings.
25	..	40	27	300	30-30-30-20-20	1600	0	0	3 equal feedings.
	..	40	27	300	10-10-10-10	1600	0	0	
	..	40	27	300	20-8-12	126	0	0	
Jan 12	..	40	27	300	24-10-14-10	224	0	0	
	..	70	102	200	24-10-(24)	266	0	0	
	..	70	102	200	14-0-0	137	0	0	
Feb 11	..				*(36)						

* Protamine zinc insulin.

necessary to give 40 units of insulin at half-hour intervals for sixteen doses, then 30 units hourly for six doses. In the first twelve hours of treatment 790 units of insulin were given, in the second twelve hours 150 units (a total of 940 units in twenty-four hours). The unusually large amount of insulin was indicated in view of the slowness of the response of the CO_2 combining power of the blood plasma and the plasma acetone (Table 8).

Carbohydrate, Liquids, Chlorides and Alkali.—One liter of 5 per cent dextrose in normal saline was administered intravenously at the outset of treatment. Eight ounces (240 cc.) of normal saline were left in the stomach after the gastric lavage. Five hundred cubic centimeters of a 2 per cent solution of sodium bicarbonate were given intravenously three hours after treatment was started. This was followed by 1 liter of normal saline intravenously, which in turn was followed by 325 cc. of a 10 per cent solution of dextrose intravenously (5 P.M.) and five hours later (10 P.M.) 1 liter of normal saline was given subcutaneously. At 1 A.M., 325 cc. of a 10 per cent solution of glucose was given by venoclysis. A liter of water and salty broth was given by mouth in the first twenty-four hours of treatment.

A diet (liquid for three days) containing 40 Gm. of protein, 300 Gm. of carbohydrate and 27 Gm. of fat (1600 calories) was begun at noon on December 25 (two days after admission). The diet was divided into six equal portions, a feeding every four hours. This was continued until December 30 when feedings at six-hour intervals were begun and finally, on January 7, the usual three-meal schedule was resumed.

The insulin was divided into the same number of doses as there were meals, and the amount given was steadily decreased as the blood sugar level became normal. When discharged, this patient was receiving 36 units of protamine zinc insulin and 14 units of unmodified insulin, both given before breakfast as separate injections.

Gastric Lavage.—The stomach was emptied of a large quantity of fluid containing minute black particles. This was done because of persistent vomiting and abdominal distention.

Enema.—A soapy water enema, which was effectual, was given early in the course of the treatment.

This illness and the past experiences of this unruly patient proved of no avail as he was readmitted on March 21, 1938, in diabetic coma of three days' duration. His blood sugar level was 380 mg. per 100 cc. and the CO_2 combining power of the blood plasma was 4 volumes per cent. In spite of 1500 units of insulin, 6500 cc. of fluids, including racemic sodium lactate solution, there was no improvement, either from the clinical or chemical point of view, and he died twelve hours after admission.

Discussion.—In both cases presented here we find that infection played a part in precipitating the ketosis. The ensuing anorexia was the excuse offered by the first patient for discontinuing the use of insulin. Ketosis is to be suspected when all desire for food is lost. This is especially so if an infection is present. When recognized early, this condition may be corrected and coma prevented. In place of solid food by mouth, the carbohydrate allowance of the diet is given in liquid form: gruels, ginger ale, orange and other sweetened

fruit juices at four-hour intervals. The total daily dose of insulin is divided into six equal doses, one being given with each liquid nourishment, every fourth hour. If liquids are not tolerated by mouth, a continuous intravenous administration of 5 per cent dextrose in normal saline may be given very slowly (1 liter in six hours) and insulin given at four- or six-hour intervals as required.

Gastric lavage was employed in one instance and not in the other. It is a valuable measure in event of persistent vomiting, abdominal distention and when abdominal pain is a prominent feature. The prompt relief from abdominal pain, tenderness and muscle rigidity which frequently ensues aids in excluding a diagnosis of an intra-abdominal catastrophe.

Bicarbonate of soda or racemic lactate solution is given to patients having a very low CO_2 combining power of the blood (below 15 volumes per cent). The amount given is calculated to raise the CO_2 combining power to a safe level, approximately 35 volumes per cent, and not to normal. This precaution we believe prevents all danger of an alkalosis and brings the calculated dose of lactate to a volume which can be safely given.

Summary.—1. Ketosis in the diabetic patient is precipitated by: (1) infections, (2) omission of insulin, (3) vomiting, (4) diarrhea, (5) neglect of the diabetes, and (6) indiscretions in diet.

2. Two cases of diabetic ketosis are reported. The first illustrates (1) the omission of insulin, because of anorexia, as a cause of impending coma, and (2) the use of a large dose of protamine zinc insulin and a large dose of unmodified insulin at the outset of treatment. No insulin was given for the ensuing twelve hours. The second case illustrates the treatment of diabetic coma with unmodified insulin given at half-hour intervals.

3. The other measures, carbohydrate intake, chlorides, fluids, warmth, enemata, gastric lavage and alkalis, are dealt with in each case report.

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THE CARDIOVASCULAR COMPLICATIONS OF DIABETES MELLITUS

SINCE the advent of insulin the life expectancy of diabetics has increased greatly, the greatest gains, of course, having been made in the younger patients. It is estimated that an increase of as much as thirty years has been gained for a diabetic child ten years of age, comparing the period of 1897 to 1913 with the period of 1926 to 1929.¹ Despite this remarkable progress, however, the death rate of diabetic patients is still much in excess of that of the general population. Patients who formerly would have succumbed from diabetes are now living to die of other conditions, to which sufferers from the disease are especially susceptible. Joslin² found that more than a fourth of all the non-coma deaths since 1922 were due to heart disease, and that arteriosclerosis in its varied forms was responsible for over half the deaths in his large group of diabetic patients.

It has been known for some time that angina pectoris and coronary thrombosis are unusually frequent in diabetic patients of the older age groups. The relatively high frequency of these diseases in women with diabetes as compared to their infrequency in non-diabetic women is striking. With the prolongation of the life span of younger diabetic patients since the advent of insulin, the acute manifestations of coronary artery disease (angina and thrombosis) have been observed with an increasing frequency in both sexes. All of these observations suggest a direct causal relationship between diabetes and coronary disease.

When we realize that at least two thirds of all cases of diabetes begin after the age of thirty-nine, and that roughly

nine tenths of the total diabetic population is above this age,³ it may be anticipated that degenerative conditions of all types will be associated frequently with this disease. In addition, because of the lengthening of the life span of diabetics and the aging of the general population, more and more patients with this disease are living to an age in which they are exposed to the risk of arteriosclerosis from causes other than diabetes.

The incidence and manifestations of arteriosclerotic changes in patients with diabetes, as determined by clinical studies and at postmortem examinations, are of interest and importance. It should be stated that arteriosclerosis *per se* is practically never a *cause* of diabetes, but that prolonged diabetes undoubtedly exerts a marked etiologic influence on the development of arteriosclerotic changes (atherosclerosis). It is estimated that more than half of the diabetics now living in the United States will die of some form of occlusive vascular disease.⁴ While the mortality from gangrene of the extremities is decreasing, that from disease of the coronary arteries is increasing. In the diabetic, degenerative disease (atherosclerosis) of the arteries is found most frequently in the vessels of the heart and extremities. This is in contrast to the frequent damage to blood vessels of the brain and kidneys by atherosclerosis in non-diabetic patients. In 484 autopsies on diabetic patients, Warren⁵ found that 30 per cent of the deaths were due to arteriosclerosis, and over half of these to heart involvement. Necropsies on sixty-one patients who were known to have had diabetes for fifteen years or more showed that thirty-five (57.4 per cent) had died as a result of arteriosclerotic lesions. Gangrene of the extremities was responsible for about only 19 per cent of the deaths from arteriosclerosis. Warren also found that cerebral arteriosclerosis was no more frequently a cause of death in diabetic than in non-diabetic patients in spite of the greater prevalence of arteriosclerosis in the former.

The common association of hypertension and arteriosclerosis long has been known. The present day views favor hypertension as an accelerator of the atherosclerotic processes rather than the arteriosclerotic changes as being a causal factor in the production of the hypertension. (Recent studies suggest that occasional cases of hypertension may result from

partial occlusion of the renal arteries by atherosclerotic plaques, by the mechanism described and proved experimentally by Goldblatt. It seems unlikely, however, that many of the cases of hypertension in man are explained on this basis.) Joslin has pointed out that the longer diabetics are observed, the more frequent is the development of hypertension among those who originally had normal blood pressures. The incidence of hypertension among diabetics, especially in the older age groups, is higher than in a similar group of non-diabetics. However, this cannot necessarily be taken as proof that either diabetes or arteriosclerotic processes are the cause of the elevation of the blood pressure. Obesity and possibly other factors may play an important part in the differences in the two groups.

A cursory review of the field of diabetes thus leaves us with little doubt as to the close and important relationship between this disease and arterial changes. A more detailed study of the cardiovascular system should therefore be of interest.

ARTERIOSCLEROSIS

The problem of arteriosclerosis in diabetes is an important and complicated one. To begin with, we are still ignorant of the cause or causes of arteriosclerosis as it is seen in non-diabetic patients. The process in the diabetic does not differ pathologically from that seen in the non-diabetic subject, except in the matter of degree and the tendency to involve certain arteries. When we realize that a great majority of diabetics are in the age group when they are already liable to arteriosclerotic changes, the difficulties become more obvious. Furthermore, obesity and hypertension are rather commonly associated with diabetes, and either or both of these conditions may have a definite deleterious effect on arteriosclerotic processes. That there is, however, a definite etiologic relationship between diabetes mellitus and arteriosclerosis is unquestioned.

Certain clinical features are of interest in the association of diabetes and arteriosclerosis. It has been pointed out by several authors that the degree of arteriosclerosis found in diabetic patients is more in proportion to the duration of the diabetes than to the age of the patient or the severity of the

diabetes. Control of the diabetes is probably also important in the prevention of arteriosclerosis in these patients. Inadequate control of the diabetes is probably a greater factor in the development of premature sclerosis than the type of diet employed. It is believed by many that the high-fat, low-carbohydrate diets given in the pre-insulin and early insulin eras tended to accelerate arteriosclerosis and that the diets in general use today in cases of diabetes may reduce the incidence of arterial disease in the future. At the present time there are not sufficient data to add much support to either view. It is significant that increasing evidence shows that diabetes of several years' duration in younger patients is accompanied by a high incidence of arteriosclerotic changes.^{6, 7}

Arteriosclerotic processes as seen in the human subject are largely of two types: (1) Atherosclerosis (intimal plaques), the characteristic lesion of elastic arteries such as the aorta and carotid arteries, and (2) Monckeberg sclerosis (medial calcification), the type seen in muscular arteries such as those of the extremities. Warren⁵ points out that the atheromatous type is the common one in diabetics, and that intimal involvement by atherosclerosis in a muscular artery, alone or with medial calcification, is very suggestive of diabetes.

The development of premature atherosclerosis in diabetic patients probably depends on several factors: There must be a considerable individual variation in the susceptibility to such processes, as is seen in non-diabetic patients. Joslin² believes that the chief cause of premature atherosclerosis in diabetic patients is "an excess of fat in the body (obesity), in the diet, and in the blood." He emphasizes the lack of control of the diabetes as an important cause of hypercholesterolemia. Rab-inowitch⁸ also believes that an excess of blood cholesterol is an important factor in the production of premature arteriosclerosis. The hypotheses of Warren⁵ in regard to the development of atherosclerosis seem quite logical. He feels that the abnormal lipid metabolism is only one factor in the development of the atherosclerotic plaque. Fluctuations in the blood sugar level and acidosis may cause osmotic pressure changes and changes in the permeability of the intima so that lipid-laden plasma penetrates the vessel wall. It would seem likely that infection and perhaps other factors unknown at

present produce changes in the intima of the vessels, rendering them more susceptible to degenerative processes. Why certain vessels like the larger arteries of the heart and extremities should be unduly liable to these changes is a matter of much interest.

In this paper we are interested primarily in the relation of diabetes to diseases of the heart and a more detailed discussion of coronary artery disease is therefore indicated.

CORONARY ARTERY DISEASE

Heart disease is the great cause of death in adult diabetic patients and its incidence is increasing. The problem of preventing cardiac disease in these patients is largely one of decreasing the incidence of coronary atherosclerosis in an attempt to reduce the occurrence of cardiac failure, angina pectoris and coronary thrombosis. A comparison of the hearts of diabetic and non-diabetic patients who have well-developed coronary disease shows no essential difference in the pathologic changes present in the arteries and suggests that the pathogenesis is similar.⁹

Clinical analysis of groups of diabetic and non-diabetic patients with coronary heart disease, however, reveals rather striking differences: Nathanson¹⁰ found severe coronary disease in forty-one of 100 autopsies on patients with diabetes mellitus. In those patients above the age of fifty, the incidence was 52.7 per cent as compared to 8 per cent in a much larger series of non-diabetic patients. The high incidence of coronary artery disease in women with diabetes mellitus is nearly proof in itself of the causal relation between diabetes and coronary sclerosis. Disease of the coronary arteries sufficient to produce clinical manifestations is very uncommon in women below the age of fifty unless diabetes or hypertension is present.¹¹ There are many data to prove the greater frequency of coronary disease in men, the ratio in the general population probably being at least 5 to 1. In diabetic patients, however, coronary disease, as represented by angina pectoris and coronary thrombosis, is nearly as frequent in women as in men.

The dramatic nature of angina pectoris and coronary thrombosis is such that one is apt to forget that the underlying pathologic condition is coronary disease and that these acute

episodes only represent a portion of the disability and deaths due to coronary heart disease. They are merely highlights in the gradual and progressive disease which is insidiously attacking the heart and which has often previously been unsuspected.

It is difficult to estimate the amount of cardiac disease due to a gradual narrowing of the larger coronary arteries without the classical picture of either arterial closure or temporary myocardial ischemia. Only the unfavorable clinical course or perhaps postmortem examination reveal the true degree of the arterial damage. The essential type of cardiac lesion in the diabetic patient is thus coronary atherosclerosis. The clinical manifestations of this process vary considerably in different patients, but the condition always tends to be progressive.

ANGINA PECTORIS

It is not within the province of this paper to discuss in detail the clinical features of angina pectoris. There has been considerable agitation in recent years to discard the term "angina pectoris" in favor of a more accurate one, because of the large number of conditions to which this term has been applied in the past.¹² The association of this term with sudden death in the mind of the laity also makes its use undesirable when speaking of cardiac conditions to patients or to their families. Present day usage limits the term "angina pectoris" almost entirely to a temporary ischemia of the ventricular muscle as a result of coronary sclerosis. It is in this sense that the word is used in this presentation.

If one excepts patients with syphilitic aortitis, angina pectoris practically always is associated with coronary atherosclerosis. It has been shown that coronary sclerosis bears a more definite relationship to the duration of the diabetes than to its severity or to the age of the patient.⁴ This seems true for patients with or without hypertension, though more extensive disease of the coronary arteries is to be expected if both hypertension and diabetes are present. Joslin² states "the frequency of angina in diabetics depends on the duration of the diabetes," and that "the incidence of angina trebles in the second ten years of diabetes." Root and Graybiel¹³ found the average age of diabetic patients with angina to be higher than

that of a non-diabetic series. In only nine of 210 cases did the angina precede the diabetes. Hypertension was present in slightly over half of these cases. In the older age group with angina some cases of diabetes are probably overlooked because of a high renal threshold with absence of glycosuria.

The following case report illustrates a number of problems in the question of angina pectoris and diabetes.

Case I.—C. H., a farmer aged sixty-two years, when first seen in February, 1935, complained of pain in the right forearm and elbow which appeared following exertion or with excitement. The family history was irrelevant. He stated that he had been in relatively good health all of his life except for arthritis, in 1919, which had subsided after the removal of an infected tooth. He had digestive disturbances at intervals from 1918 to 1922, suggesting a peptic ulcer. In September, 1932, he was rejected for life insurance because of obesity. In December, 1932, he consulted his family doctor because of a draining ear. At this time glycosuria was discovered. His weight had reached a maximum of 205 pounds. The diabetes was fairly well controlled by restrictions in diet, and a considerable reduction in weight ensued.

In June, 1933, because of persistent gastro-intestinal symptoms, he was admitted to the Pennsylvania Hospital. Barium studies of the gastro-intestinal tract revealed nothing abnormal, but a roentgenogram of the gallbladder showed poor concentration of the dye and a mottling of the shadow, suggesting multiple non-opaque calculi. Despite a diet containing only 1400 calories per diem, small doses of insulin were needed to control the diabetes. An operation was performed under spinal anesthesia, and a chronic cholecystitis was found with an early cirrhosis of the liver. Cholecystostomy was performed. The convalescence was uneventful. At the time of discharge from the hospital he weighed 145 pounds. He was taking 30 units of unmodified insulin a day and the diet contained 60 Gm. of protein, 150 Gm. of carbohydrate and sufficient fat to make a total of 1400 calories. The heart was slightly enlarged to the left and a moderately loud systolic murmur was audible at the apex. The systolic blood pressure was 120 mm. of Hg, the diastolic 70 mm.

The patient continued to improve after a few months, and the diabetes was well controlled without insulin. In February, 1935, he was referred to a consultant because of severe pain in the right arm. At that time he gave the following additional history. For a period of at least five years he had noted a rather severe pain in the right forearm which would come on with exertion or after excitement. These "attacks" had become more frequent and severe, and in the fall of 1934 he began to be awakened at night by the pain which would last for several minutes. There was no soreness in the muscles or numbness of the extremity. A typical severe attack began in the right infraclavicular area and spread to the shoulder and down the inner aspect of the arm to the upper forearm. In a few very severe attacks the pain spread up the right side of the neck and along the mandible. There was never any pain noted over the heart, sternum, or down the left arm. Occasionally, attacks had come on when he was quiet but usually they were precipitated by exertion and he would be forced to become inactive because of the severity of the distress. He felt certain he could precipitate an attack of pain by walking rapidly, but did not desire to do so. He stated that he did not overeat, as

had been his previous habit. Prior to the removal of his gallbladder he had vomited with a few of the more severe attacks, but this had not occurred since operation, though the pain was more severe. He was concerned by the increasing frequency and severity of the attacks which would last several minutes. There was no significant shortness of breath and no cough or edema.

Physical Examination.—Physical examination in February, 1935, revealed a slightly overweight (155 pounds) plethoric male of stated age. His pupils were normal and there was no arcus senilis. The ocular fundi showed definite arterial changes but no hemorrhages or retinitis. The remaining teeth were in fair condition and the tonsils were small. His chest was the short, thick type, and the lungs were clear. The apex beat was felt in the fifth left interspace 14 cm. from the midline (mid-clavicular line 10 cm.). The left border of cardiac dullness extended 12 cm. from the mid-sternal line and the right border 2 cm., in the fifth interspaces. The cardiac rhythm was regular and the rate was 64 per minute. A moderate systolic murmur was heard at the apex transmitted to the axilla. A systolic murmur was heard at the base, with greatest intensity at the aortic cartilage. The blood pressure was 170/90 on the right and 174/88 on the left. The abdomen was obese and relaxed. The liver edge was felt 3 cm. below the costal margin in the right mid-clavicular line; the spleen was not felt. The extremities were not remarkable except for moderate peripheral arteriosclerosis. Examination of the urine revealed a specific gravity of 1.026 and only a trace of albumin and a few hyaline casts. There was no glycosuria.

Electrocardiogram.—There was a marked left axis deviation. Diphasic T waves were present in Leads I and II with upright (abnormal) T waves in the precordial lead (old Lead IV).

Clinical Diagnosis.—Obesity, diabetes mellitus (history), generalized arteriosclerosis, coronary artery disease with cardiac enlargement and angina pectoris.

Clinical Course.—The patient was digitalized, with no improvement or aggravation of symptoms. He was then given nitroglycerin (gr. $\frac{1}{200}$) to be taken during the attacks of pain in the right shoulder and arm. This drug produced almost immediate relief from the pain and was the first therapy which had proved effective in this regard. He continued to have the attacks of pain when his activity was not considerably curtailed until early in June, 1935, when he was taken with severe, persistent, precordial and substernal pain with dyspnea and cyanosis. A clinical diagnosis of coronary thrombosis was made by the family physician and he was confined to bed. After two weeks the patient refused to stay in bed and was up and about for a few days. He became worse rapidly, however, with obvious beginning cardiac failure and he returned to bed, where he died rather suddenly on July 6th.

This rather involved case illustrates a number of interesting points. The wisdom of the life insurance company in rejecting him because he was considerably overweight was amply confirmed. Joslin and others have stressed the fact that obesity is the greatest exciting factor which will help bring out the inherited disposition to diabetes mellitus. A mild diabetes may have persisted in this patient for some time before the glycosuria was discovered. The angina pectoris was atypical

in the distribution of the pain, but the attacks were precipitated by the usual factors and relieved by nitroglycerin. A fatal outcome after coronary occlusion closes the picture in the manner in which so many diabetic patients succumb.

CORONARY THROMBOSIS

For practical purposes, sudden occlusion of the coronary arteries may be regarded as a thrombosis occurring at the site of previous damage to the intimal lining of the vessel. Coronary thrombosis is about twice as frequent in diabetic as in non-diabetic patients of the same age group. Root¹⁴ reports that, between the ages of forty and sixty years, in 23 per cent of 132 autopsies on diabetics coronary occlusion was found. This is contrasted with 6 per cent found in 1273 autopsies on non-diabetics of the same age group.

This high incidence is due probably entirely to the frequency and severity of coronary atherosclerosis in diabetes mellitus. The association of obesity and/or hypertension with diabetes probably adds further factors favoring the development of degenerative coronary disease. The high incidence of coronary thrombosis in diabetic women is further evidence for the close association of diabetes and coronary artery disease. Root and Sharkey⁴ found thirty-two cases of coronary occlusion in 175 *diabetic* patients (100 women and 75 men). Eighteen of these were women and fourteen were men, a ratio of practically 1 to 1. This ratio of women to men is most unusual and is not seen in autopsy series of non-selected cases of coronary occlusion.

In the last 100 consecutive cases of myocardial infarction resulting from coronary occlusion at the Pennsylvania Hospital, there were eighty-one men and nineteen woman, a ratio of 4 to 1. A brief analysis of the *female* cases is of interest. Five of the nineteen women had diabetes. The youngest patient, a diabetic, had her first coronary occlusion at forty-four years of age, and a second fatal attack at forty-six years of age. Of four patients, fifty years of age or younger, three had suffered from diabetes and the other had severe, long-standing hypertension. The other two diabetic patients were aged sixty-five and sixty-nine years. The average age of all the female patients was fifty-nine years. Excluding the diabetics,

the average age was sixty-five years. Twelve of the nineteen patients had arterial hypertension, including two of the diabetics.

In Warren's large series of postmortem examinations on diabetic patients death was attributed to cardiac infarction in 16.4 per cent, and 41 per cent of these were in women! In addition, there were ten cases in which death probably resulted from coronary occlusion but a fatal issue occurred before there was time for infarction of the muscle. This high incidence of cardiac infarction is more evident when the figures are compared with a large general autopsy series. In a careful study of the hearts in 1000 consecutive autopsies Barnes and Ball¹⁵ found forty-nine with old or recent localized infarcts, an incidence of 4.9 per cent. In 1750 autopsies, about 1000 of which were coroners' cases, Benson and Hunter¹⁰ found a total of seventy-two infarcts and cardiac aneurysms (4.1 per cent). There were an additional 3 per cent (fifty-four cases) with fresh thrombosis but without infarction. This unusually high incidence of acute occlusion without infarction was no doubt due to the large number of cases of sudden death which would be found in such a series. The number of diabetics in the group was not known.

Thus it seems well established that the incidence of coronary thrombosis with infarction of the heart muscle is unusually frequent in diabetic patients. This is especially true in the group of older patients with diabetes, usually mild, who are already in the arteriosclerotic age group.

The clinical picture of coronary thrombosis may be complicated by the development of coma in a diabetic patient. The occurrence of fever, increased metabolism, and gastrointestinal upsets may all predispose to the development of coma in a diabetic patient who has developed this complication. The occurrence of cardiac infarction in a diabetic patient is not a signal to stop previous insulin therapy or a contraindication to the institution of insulin therapy in a previously mild diabetic, if acidosis is developing. It is possible that a sudden lowering of the blood sugar by insulin therapy may predispose the patient with coronary disease to thrombosis in the coronary arteries. There is some clinical evidence supporting this view,¹⁷ but it seems unlikely that this is a frequent cause of

coronary artery occlusion. The whole problem is deserving of further study before definite therapeutic theses are developed.

TREATMENT

In the discussion of the treatment of the cardiovascular complications of diabetes mellitus, too much stress cannot be laid upon *preventive* measures. The one great therapeutic problem is to reduce the incidence of atherosclerosis of the coronary arteries. In no other way can the rising death rate from cardiovascular disease be checked. The problem of preventing or delaying the development of coronary sclerosis is a complex and difficult one. It must be remembered that a majority of diabetics are already in the older age group.

Careful and constant control of the diabetes, year in and year out, is probably the most important single factor in this preventive program. This may entail the use of insulin for some patients who might ordinarily "get by" without it. The occasional checking of the fasting and post-prandial blood sugar levels is of importance to be certain that the diabetes is well controlled. A high renal threshold may prevent glycosuria and give the false impression that the diabetes is well controlled. If the diabetes is poorly treated, there is a tendency toward hypercholesterolemia, no matter what diet the patient may be taking, though hypercholesterolemia is more frequent when the diet contains high fat and low carbohydrate quotas. A high fat content of the blood serum is thought by several authorities to be the most important factor in the development of degenerative arterial disease in diabetics.

In overweight diabetics (who almost invariably are mild cases), a reduction of weight is of the greatest value. These features are stressed by Durkin and Fetter. There may be considerable difficulty in controlling the diabetes, even though mild, unless there is a reduction in weight. Insulin is remarkably ineffective when given to obese diabetic patients unless a low caloric diet is used simultaneously. If a low caloric diet is instituted, insulin is not necessary, except during the course of acute complications. A relatively high carbohydrate diet is used when an undernutrition regimen is employed, as the patient will be metabolizing body fat for some of his caloric requirements. Sufficient protein is given to maintain a nitro-

gen balance. Such a diet would contain, for example: protein 60 Gm., carbohydrate 180 Gm., and fat 25 Gm. (approximately 1200 calories). Insulin may be required at the beginning of treatment if there is an acute complication, but usually the diabetes can be readily controlled in these obese patients by diet alone.

A reduction in weight is also of value in the treatment of arterial *hypertension* which is so common in the obese patient suffering from diabetes. This condition is less apt to develop as the diabetic grows older if the weight is kept close to the normal level. *Hypertension per se* is undoubtedly a great accelerator of atherosclerotic processes, so its occurrence in a diabetic patient is unfavorable.

Several investigators have advocated the use of a "high-carbohydrate, low-fat diet" to prevent hypercholesterolemia and thus lessen the tendency to develop vascular sclerosis. These diets are in general use today, but it is too soon to determine whether or not they will prove effective in this regard. The lack of control of the diabetes is a greater factor in causing hypercholesterolemia than the diet itself.¹⁸

Insulin therapy in patients with known or suspected *coronary artery disease* should be conducted cautiously. The diseased heart probably requires a greater amount of carbohydrate than the normal one, despite the fact that the heart muscle of diabetic patients has as much or more glycogen than that of normal persons. Nevertheless, a rapid lowering of the blood sugar may produce symptoms in such patients even though the actual level reached would not be considered abnormally low in a normal individual. For practical purposes, insulin is not contraindicated in these cases and it should be used when needed, but care should be exercised to avoid a rapid lowering of the blood sugar. Some authorities believe that patients of this type do better with a blood sugar slightly above the normal level. It is doubtful, however, if this is a good general policy. Allen and Duncan insist that hyperglycemia be prevented but caution against rapid changes in the blood sugar level.

Considering all angles of the question, there is certainly inestimable harm done by lack of careful control of the diabetes. Control of the diabetes, on the other hand, is para-

mount in the prevention of the progressive tendency of the degenerative processes.

In the treatment of diabetic patients with *cardiac failure* from any cause, the use of a low-caloric diet is indicated. A soft diet, high in carbohydrates, usually is taken best. Small and frequent meals are frequently used. Insulin, if employed, should be continued but should be increased or decreased as indicated by the presence or absence of glycosuria and by the level of the blood sugar. Diabetes presents no contraindications to the usual measures employed in the treatment of heart failure.

Angina pectoris occurring in a diabetic patient calls for a gradual control of the diabetes. Root and Graybiel¹³ found that those diabetics suffering from angina who died within the first year after its onset were largely those having received conspicuously little treatment. The condition of patients with poorly-treated diabetes and angina is improved by careful and gradual regulation of the diabetes. Sudden reductions in the blood sugar level are not well borne by these patients, however.

Coronary thrombosis is not a contraindication to insulin therapy. In diabetics who previously have needed insulin the requirement is usually temporarily increased. The signs and symptoms of coronary thrombosis in some cases may be masked by the development of ketosis and coma. Great care should be taken in the conduct of treatment to avoid even mild degrees of hypoglycemia. In fact, during the first few days a mild degree of hyperglycemia will do no harm and will increase the margin of safety.

For the patient having a mild diabetes and coronary artery occlusion, a diet similar to that recommended by Master¹⁹ for the treatment of non-diabetic patients is used. It contains approximately 250 Gm. of carbohydrates, two thirds of a gram of protein per kilogram of body weight, and sufficient fat to make a total of 15 calories per kg. For patients with a more severe diabetes where control of the diabetes may be difficult, the use of equally-divided and equally-spaced feedings with the same amount of insulin given before each feeding is best employed. This treatment is outlined elsewhere in detail in this symposium. This regimen, advocated by Duncan,²⁰ is a very effective and safe means of controlling severe diabetes

in the presence of acute complications, whether surgical or medical in type.

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DIAGNOSIS AND TREATMENT OF CONGENITAL OR PRENATAL SYPHILIS

THE problems of prenatal or congenital syphilis, for present-day usage makes the terms more or less interchangeable, are as multiform and varied as are those of the acquired forms of the disease. Congenital syphilis, through the inevitably increased grist of the operation of blood-testing laws, will become a more and more important field of medical diagnosis and treatment. It is, in addition, the field *par excellence* for a demonstration in preventive medicine. The recognition and treatment of the disease in the pregnant woman protects the child; and the increasingly early and effective management of the disease in the infected newborn and young child protects the adolescent and the adult.

From the many problems which the field presents today, we have selected seven cases as illustrations; four of them are concerned with the pregnant woman and the young syphilitic child, and three of them with manifestations of so-called "tar-dive" congenital syphilis in the older child and in the young adult. The four cases of the first group will be presented by Dr. Ingraham, with our joint summary and commentary, and the three cases of the second group by Dr. Stokes:

THE PREGNANT MOTHER AND THE YOUNG SYPHILITIC CHILD

Case I. The Mother Who Acquires Syphilis and Becomes Seropositive During the Pregnancy.—B. D., a twenty-seven-year-old white woman, came under medical observation in the sixth month of her first pregnancy. Complete physical examination, performed by the obstetrician, revealed no evidence of syphilis and a blood serologic test taken on the first prenatal

visit was reported Kahn negative, Kolmer Wassermann negative. Six weeks before delivery this patient became ill at home with a sore throat and a slight temperature elevation to 99.5° F.; she developed a number of discrete, dusky-red papular lesions over her face and upper chest and some two to three weeks later, several small papular genital lesions.

Prior to the development of this eruption she had contracted an acute upper respiratory infection and had been taking, internally, salicylates, barbiturates and phenolphthalein. Reference was made to the previous blood serologic test which was found to be negative. A second blood study was considered unnecessary. The symptomatology presented was considered to be erythema multiforme from bacterial infection or a dermatitis medicamentosa from ingested drugs. The fact that the mother in actuality had secondary syphilis was not disclosed until she gave birth to her infant on February 12. The infant manifested symptoms of congenital syphilis within forty-eight hours after birth and its infection was immediately diagnosed and treatment was begun (Table 1). Both mother and child have had a satisfactory clinical response.

Most active obstetrical services, particularly those of a large general hospital, or those which care for many unmarried mothers or sexually promiscuous women, will have several instances yearly in which women, symptom-free and serologically negative early in the pregnancy, develop clinical syphilis or become seropositive before term. In some instances the disease has been acquired at the time of conception, the ameliorating effect of pregnancy on maternal syphilis frequently causing a prolonged incubation period and often a relatively symptomless infection. In other cases the disease is acquired through sexual relations in the early months of pregnancy, to become clinically manifest close to the time of delivery and, rarely, in the first week or two postnatally.

All such women have early syphilis, and are not only important public health problems from the standpoint of the community at large, but also, because of the active spirochetemia attending this stage of the disease, important progenitors of congenitally syphilitic infants since they almost never give birth to healthy offspring. The commencement of prenatal antisiphilitic therapy immediately in such cases, while it cannot always assure the birth of a non-syphilitic infant, will often prevent a stillbirth or neonatal death, giving a living and treatable, if diseased, child. It will also make the danger of infection to the obstetrician, through operative mishap, less.

To detect the majority of these cases in which syphilis is acquired during pregnancy, it has been recommended that every parturient woman have a blood serologic test, not only

TABLE 1

TYPES OF THERAPY USED IN SUCCESSFULLY TREATING INFANTILE CONGENITAL SYPHILIS IN CASE I (CLINICALLY MANIFEST DURING NEONATAL PERIOD) AND CASE II (POSITIVE BLOOD SEROLOGIC DIAGNOSIS AT AGE 3 MONTHS). SEE TEXT FOR MORE DETAILED DISCUSSION

Case I

Date.	Injection number.	Drug	Dose.	Blood serology.			Weight.
				Kahn.	Kolmer.	Kline.	
2/14	1	Sodium bismuth tartrate, 1.5% (1 cc. — 11 mg. bismuth metal).	0.2 cc.	—	—	4+	6 lb.
				(darkfield positive, cutaneous lesions)			
2/18	2		0.3	44	444	4+	
2/21	3		0.4				
2/24	4		0.5				
2/25	5		0.5				
3/3	6		0.5				
3/10	7		0.5				
3/12	1	Bismarsen (bismuth arsphenamine sulfonate).	0.03 Gm.				8 lb.
3/18	2		0.03				
3/25	3		0.03				
4/1	4		0.03				
4/8	5 to		0.03				
5/19	11		0.03				8 lb., 4 oz.
5/26	12 to		0.03				9 lb., 11 oz.
6/23	16		0.04				
6/30	17 to		0.04				
9/1	24 to		0.05				
12/15	40		0.05	00	000	neg.	11 lb.
			0.05	00	000	neg.	
12/22 to	1	Bismuth subsalicylate (1 cc. — 60 mg. bismuth metal)	0.5 cc.				18 lb.
2/9	8		0.5 cc.				
4/14		Cerebrospinal fluid—cells 3; Wassermann 0000; Pandy 0; colloidal mastic		00	000	neg.	1100000000

Case II

9/3							
9/12							
9/19 to	1	Bismuth subsalicylate (1 cc. — 60 mg. bismuth metal).	0.25 cc.	4+	4+	—	10 lb., 2 oz.
11/5	8		0.25 cc.				
11/12 to	1	Sulfarsphenamine.	0.06 Gm.				
12/31	8						12 lb., 4 oz.
1/7 to	1	Bismuth subsalicylate	0.06	1+	neg.	—	
2/2	8		0.33 cc.				14 lb.
			0.33 cc.				
3/10 to	1	Sulfarsphenamine.					
4/28	8		0.08 Gm.				14 lb., 10 oz.
			0.08	neg.	neg.		

Continue in alternating courses of sulfarsphenamine and heavy metal: 8 injections to course for one year if serologic response is satisfactory. Dosage calculated according to weight of child. Always finish course of treatment with a heavy metal.

at the time of the first prenatal visit, but also in the eighth month of the pregnancy. This latter recommendation, of course, presupposes that the date of termination of the pregnancy is always known or readily calculable, when in actuality

this estimation will frequently become an insurmountable difficulty in the average prenatal clinic. Certainly if the pregnant woman has had no check for syphilis in late pregnancy (and in most instances even if she has), she should have a complete reappraisal at the time of delivery, including a physical examination with the thought of syphilis uppermost in mind and an *arm venous blood Wassermann*, for which a cord Wassermann (on the child's blood), in that it is frequently negative in the presence of an active infection of the mother, is no substitute.

The medical treatment of this syphilitic child will be considered in the comment following Case II.

Case II. The Syphilitic Mother with Doubtful or Negative Serology During Pregnancy.—H. G. was a twenty-three-year-old, apparently healthy colored primipara. Initial physical examination performed in the second month of her pregnancy showed no evidence of syphilis, but a blood serologic test, reported November 7th, revealed Kahn plus minus, Kolmer Wassermann 1 plus, Noguchi Wassermann negative. Complete reappraisal of the situation on November 21st showed negative physical findings and repetition of the blood serologic tests showed Kahn 1 plus, Kolmer Wassermann negative, Noguchi Wassermann negative. Family investigation revealed the fact that the patient had been married for three years, and that her husband had been discovered in routine medical study one year previously to have latent syphilis of unknown duration, for which he had been treated actively since. The patient herself had never been diagnosed as having syphilis and was never treated.

On the basis of the above facts syphilologic consultation recommended as follows: "This case, presenting a weakly positive Wassermann reaction early in her pregnancy, when her husband is known to have syphilis, presents something of a problem. To be absolutely certain that the child will be healthy it would probably be better to treat her during her pregnancy. On the other hand, the diagnosis of syphilis *in her* has not been established and it is probably unwise to subject a patient to a long series of relatively toxic treatments on so little evidence. Would accordingly advise withholding treatment for the time being and recommend monthly check-up until delivery."

This monthly reexamination was carried out, blood serologic tests revealing:

Date.	Kahn.	Kolmer.
11/28..	Negative.	Negative.
12/12....	Negative.	Negative.
1/9....	Negative.	Negative.
2/13....	Negative.	Negative.
3/20....	Negative.	Negative.
4/17....	Negative.	Negative.
Maternal blood at delivery 6/12	Negative.	Negative.
Cord blood at delivery 6/12....	Negative.	Negative.

In consequence, no treatment was given prenatally. The infant was normal at birth and remained so until October 3rd (twelve weeks old) when he developed generalized lymphadenopathy and tenderness of the long bones. A roentgenogram showed skeletal changes indicative of congenital syphilis, and a blood serologic test on the infant showed Kahn 4 plus, Kolmer Wassermann 4 plus, confirmed October 12th. Treatment of both mother and child was begun on October 19th (see Table 1 for infant's treatment) and has been carried through to successful conclusion in each instance. The maternal Wassermann at the time of onset of therapy showed Kahn 1 plus, Kolmer Wassermann negative, with no symptoms of infection.

In the average large prenatal clinic from 15 to 20 per cent of the syphilitic women will be seronegative. Many of these women will give birth to syphilitic infants if they are permitted to go through their pregnancy untreated, particularly if their disease is of less than ten years' duration and if they have had relatively little antecedent therapy.

The chance of the infant being infected is so great that it is usually considered advisable to treat actively any such woman in whom the disease has been definitely diagnosed provided: (1) she has had no serious reaction from previous antisyphilitic therapy, (2) she has had no evidence of toxemia in previous pregnancies, and (3) if studies of her general medical condition and eliminative mechanism indicate she is eligible for arsenical and heavy metal treatment during her pregnancy.

If the seronegative syphilitic woman has had difficulty under any of the three foregoing captions, her situation must be strictly individualized and, if from the combined clinical judgment of the syphilologist and obstetrician it appears that the risk for the mother from treatment is appreciable and the risk for the child slight, prenatal treatment should be withheld but active postnatal follow-up of the infant should be insisted upon.

If it be considered that a weakly positive, blood serologic test, unsupported by any definite history or physical signs of syphilis in the patient, is insufficient evidence to establish a diagnosis of the disease or to warrant active therapy, the fact that a woman is pregnant should make no exception to this statement. To find one marital or sexual partner the victim of this disease while the other has escaped is not an uncommon occurrence in conjugal syphilis studies. There is no reason, therefore, to treat a prospective mother for syphilis because

her husband is known to have the disease. Women who present doubtful or weakly positive Wassermann reactions during their pregnancy, with no other evidence of infection, will in the vast majority of instances show no evidence of the disease even on prolonged subsequent study. This situation is no different than is encountered in the doubtful reactions exhibited occasionally by non-pregnant healthy individuals or syphilis suspects in whom the disease is never proven. To subject such an individual to antisyphilitic therapy submits him to all the risks of treatment with relatively toxic and expensive drugs, without ever being certain that he has the disease, and this is probably unjustifiable.

In the majority of instances in which this disease presents a negative blood serologic test and the evidence for the existence of an active infection is even doubtful, the situation in respect to the newborn infant can be handled satisfactorily, as in the present case, with the usual postnatal follow-up.

Treatment of Infantile Congenital Syphilis.—The variety of the drugs employed and the multiplicity of modes of administration of these remedies are sufficient evidence in themselves that there is no recognized standard therapy for congenital syphilis. The trivalent arsenicals, neoarsphenamine, old arsphenamine (606), mapharsen (arsenoxide), sulfarsphenamine, and bismarsen (bismuth arsphenamine sulfonate), sometimes given intramuscularly and sometimes given intravenously or under the fascia of the scalp; a pentavalent arsenical, acetarsone (stovarsol), and various bismuth and mercury compounds, given by mouth; water-soluble, oil-soluble, and oil-suspended bismuth compounds given intramuscularly; and even mercury rubs—all have their advocates under special circumstances.

No attempt has been made, accordingly, to present a standard treatment for the control of infantile congenital syphilis, but two types of treatment with which we have had extensive experience, and which were used to treat successfully the offspring in Cases I and II, are presented in Table 1. Conservative opinion suggests the following helpful basic principles guiding the therapy of these cases:

1. Treatment should be begun only when the presence of the disease in the infant is established. On an average even

an untreated syphilitic woman will have one chance in six for a healthy child. Women who have had syphilis for a long period prior to conception, or who have had varying amounts of prenatal therapy, have much less chance than this of giving birth to an infected child. In a prenatal clinic in which the average time for commencement of prenatal antisyphilitic therapy is between the sixth and seventh month, there will seldom be more than 30 per cent syphilitic infants, and frequently the figure will be much lower than this. It seems unwise to subject as many as 70 per cent of healthy infants to therapy, and it is accordingly wiser to establish the diagnosis definitely before commencing treatment.

2. There is, at the present time, no adequate substitute for injection therapy in appropriate dosage. Mercury rubs may be employed if no other form of treatment is available. Acetarsone, while producing apparently good clinical results in some cases, in addition to being an untried drug so far as late accomplishment is concerned, must be considered relatively toxic if given in adequate dosage. The problem of regulating the dosage of an oral medication administered for a disease as serious as congenital syphilis by a mother with little or no training in the necessity for scientific accuracy, will probably always remain an insurmountable difficulty (cf. Pillsbury's and Perlman's experience*).

3. No infant is too young or too small to receive antisyphilitic therapy, but the initial dosage must be conservative, particularly if the disease is clinically manifest. Congenital syphilis is a much more massive and intoxicating infection than is ever encountered in the adult. Therapeutic shock and therapeutic paradox are to be feared, and may result in the permanent crippling or death of the infant if treatment is too vigorous at the start. It seldom is desirable to begin treatment with the arsenical, though it may be employed in a dosage of approximately one tenth the calculated dose by weight for the first two to three weeks. It is best to give, in most instances, a preparatory course of either water-soluble or oil-suspended heavy metal before introducing the relatively faster acting

* Acetarsone Therapy in 187 Cases of Congenital Syphilis, with Observations on a Group of Eighty-Seven Patients Receiving No Treatment. *Arch. Derm. and Syph.*, 39: 969 (June), 1939.

spirillicidal drugs. Even of the heavy metal, a sick infant should not receive more than one half to one quarter of the maximum dose, calculated by weight for the first ten to fourteen days. *Full dosage* should roughly conform to the following:

Bismarsen (bismuth arspenamine sulfonate):

3.5 mg./lb. (7 mg./Kg.) of body weight—once weekly.

Sulfarsphenamine:

5 mg./lb. (10 mg./Kg.) of body weight—once weekly.

Neoarsphenamine:

5–7.5 mg./lb. (10–15 mg./Kg.) of body weight—once weekly.

Bismuth Compound:

1–2 mg./lb. (2–4 mg./Kg.) of body weight of bismuth metal weekly.

(If water-soluble heavy metal is used, injections must be given at least twice weekly, and dosage so calculated as to conform to the above standard.)

4. Treatment should be continuous without a rest interval, and in alternating courses of arsenical and heavy metal (unless bismuth arspenamine sulfonate is employed), for approximately *one year*. Most patients who survive the first few weeks of therapy will have a satisfactory clinical and serologic response by this time. Persistently positive serology, positive spinal fluid, or other evidence of progression of the disease requires strict individualization, and consultation, and cannot be subjected to standard or routine procedure.

Case III. Adequate Prenatal Treatment and the Seropositive Non-syphilitic Infant.—M. M. was a nineteen-year-old, apparently healthy colored primipara. She proved to have latent syphilis of unknown duration, showing positive serology (Kahn 4 plus, Kolmer Wassermann 4 plus, Noguchi Wassermann 4 plus) on December 26th. This was confirmed January 2nd. She began neoarsphenamine therapy in the sixth month of her pregnancy and received nine injections before delivery as follows:

Date				Date			
1–2	Neoarsphenamine	0.2	Gm.	2–6	Neoarsphenamine	0.45	Gm.
1–9	"	0.3	"	2–13	"	0.45	"
1–16	"	0.45	"	2–20	"	0.45	"
1–26	"	0.45	"	2–27	"	0.45	"
1–30	"	0.45	"				

On March 13th she was delivered of a living and apparently healthy infant weighing 6 lb. 1 oz.; at this time her arm venous blood showed Kahn 4 plus,

Kolmer Wassermann 4 plus, Noguchi Wassermann 4 plus, and the cord blood was reported Kahn 4 plus. Kolmer Wassermann 4 plus, and Noguchi Wassermann 4 plus. Darkfield examination of scrapings from the umbilical vein were negative and a roentgenogram of the long bones when the infant was five days old showed no evidence of congenital syphilis. The infant's Wassermann on March 18th (five days old) showed Kahn plus minus, Kolmer Wassermann 4 plus. The infant was normal to P.E., but presented Kahn 1 plus, Kolmer Wassermann 1 plus on April 9th. The infant's physical examination and blood serologic test were completely negative on May 7th. The untreated child, followed now for forty-eight months postnatally, has remained symptom-free and seronegative.

Table 2 suggests a form of standard prenatal therapy which has been applied to the case under discussion and which is

TABLE 2

TREATMENT OF PREGNANCY WITH LATENT SYPHILIS OF UNKNOWN DURATION (UNCOMPLICATED)

Week of pregnancy.	Lunar Month.					
	1 to 4.	5.	6.	7.	8.	9.
1)	Varying amounts NS & Bi Bi 2 cc.			NS = Neocarsphenamine. Bi = Bismuth subacetylate (60 mg. bismuth metal per cc.). Dosage calculated for 150 pound individual.		
to 16)						
17)						
18)	Bi	Bi 2 cc.				
19)	Bi	Bi				
20)	Bi	Bi				
21)	NS 0.45	NS 0.3	NS 0.2			
22)	NS	NS 0.45	NS 0.3			
23)	NS	NS	NS 0.4			
24)	NS	NS	NS 0.45			
25)	NS	NS	NS	NS 0.2		
26)	NS	NS	NS	NS 0.3		
27)	NS	NS	NS	NS 0.4		
28)	NS	NS	NS	NS 0.45		
29)	Bi 2 cc.	Bi 2 cc.	Bi 2 cc.	NS	NS 0.2	
30)	Bi	Bi	Bi	NS	NS 0.3	
31)	Bi	Bi	Bi	NS	NS 0.4	
32)	Bi	Bi	Bi	NS	NS 0.45	
33)	Bi	Bi	Bi	Bi 2 cc.	NS	NS 0.2
34)	Bi	Bi	Bi	Bi	NS	NS 0.3
35)	NS 0.45	NS 0.45	NS 0.45	Bi	NS	NS 0.4
36)	NS	NS	NS	Bi	NS	NS 0.45
37)	NS	NS	NS	NS 0.45	NS	NS
38)	NS	NS	NS	NS	NS	NS
39)	NS	NS	NS	NS	NS	NS
40)	NS	NS	NS	NS	NS	NS

applicable to the usual problems of syphilis complicating pregnancy. It must be emphasized that only cases of latent syphilis and pregnancy *uncomplicated* may be routinized; all others must be strictly individualized. The term "latent syphilis," implies that the patient has had a complete examination for syphilis and no evidence of the disease is found.

The presence of symptomatic syphilis, the age of the patient, complications of pregnancy, evidence of intolerance to antisyphilitic drugs, and other factors may necessitate important modifications in this suggested system. Adherence to the following general principles, on the other hand, should always be as close as possible:

1. After the midpoint of the pregnancy is reached, the sooner the placenta becomes impregnated* with a strongly spirillicidal drug (*e.g.*, neoarsphenamine), the more likely one is to obtain a healthy child.

2. Thus, bismuth may be used up to the sixteenth to twentieth week of gestation, but the arsenical should always be commenced by the second half of the pregnancy, when the real danger of infection of the fetus begins.

3. If the woman reports after the fifth lunar month, treatment should be *commenced* with the arsenical in cautious but increasing dosage. The first injection may be 0.2 Gm. of neoarsphenamine (or its equivalent); the average dosage for the first three weeks should not be more than 0.3 Gm. of neoarsphenamine per week, and the total weekly dosage need never exceed 0.45 Gm. of neoarsphenamine, for the 150 pound adult.

4. After the fifth lunar month the bismuth course should not exceed five or six weekly injections, lest infection of the fetus result from a lack of strong spirillicide.

5. Giving an arsenical for one month prior to term makes the delivery safer for the obstetrician and employs a powerful spirillicidal drug when the protective placental membrane is thinnest† and the danger of infection of the fetus greatest.

* F. P. Underhill and F. G. Amatruda (The Transmission of Arsenic from Mother to Fetus. *J.A.M.A.*, 81: 2009 [Dec. 15], 1923), N. J. Eastman (The Arsenic Content of the Human Placenta following Arsphenamine Therapy. *Obst. and Gynec.*, 21: 60 [Jan.], 1931) and F. F. Synder and H. (The Placental Transmission of Neoarsphenamine in Relation to the Pregnancy. *Am. J. Obst. and Gynec.* 36: 579 [Oct.], 1938), all have that, while arsenic gains access to the fetal tissues in small amounts, early in the latter months of the pregnancy, it is stored in large amounts in the placenta, the amount stored increasing with the quantity and duration of therapy. It has been suggested that the greater concentration of arsenic in the placental tissues acts as a barrier, as it were, to the passage of arsenic from mother to child.

† It is apparently well recognized that the membrane which separates the maternal from the fetal circulation in the placenta is several cells wide in early pregnancy, but becomes thinner in late pregnancy with the atrophy of the so-

6. Alternating treatment is preferred to concurrent treatment. The advantage to be derived from concurrent treatment, even when the woman reports in the last months of pregnancy, is questionable when the only slightly better results with the offspring are weighed against the danger to be derived from overburdening the already taxed eliminative mechanism of the mother. A complication resulting at this point might necessitate a complete cessation of all therapy at the stage when it is most essential.

According to the experience of the Philadelphia General Hospital, about 20 per cent of the offspring of syphilitic mothers who are seropositive at the time of birth, will, on adequate postnatal follow-up, never be shown to have syphilis. Approximately 9 per cent of the non-syphilitic offspring of syphilitic mothers will be seropositive at the time of birth. The seropositive non-syphilitic infant results when there is a transfer of syphilitic reagin from the blood of the mother to the blood of the fetus in utero, without an actual infection of the fetus. Although the concentration of reagin obtained from the blood of the newborn child depends, in part at least, on the concentration of this substance in the maternal blood, quantitative titred Wassermann studies performed by others (Faber and Black, 1936; Christie, 1938) and by us during the last two years have indicated that when this transfer occurs, there is seldom more than 2-4 units of reagin in the newborn infant's blood stream. High titres obtained occasionally from cord blood specimens usually rapidly fall to this level in the infant's blood. Although this is sufficient to give a strongly positive test in the average laboratory, it usually rapidly disappears from the infant's blood stream, which will seldom give a strong positive in a non-syphilitic infant after the first three weeks of life. Cases of non-syphilitic infants which show a decreasing positive titre over a period of thirty to ninety days after birth are distinctly exceptional.

A confirmed, strong positive in an infant one month of

called Langhans cell layer between the fourth and the sixth months, so that, finally, the villi are covered only by a thin and senile syncytium. It has been thought that this order of events is important in rendering the invasion of the fetus by *Sp. pallida* more likely in the latter months of pregnancy. (Cf. A. C. Beck and W. T. Daily. Syphilis in Pregnancy, in "Syphilis and its Complications" No. 6. Am. Assoc. Adv. Sci., 1938, p. 101.)

establish a diagnosis of syphilis or as a basis for instituting treatment. Otherwise, bismuth lines (Fig. 94, C, D, E) from prenatal treatment and changes in bone growth resulting from atrophy of disease, or nutritional disturbances, usually easily differentiated by the experienced, may form the basis for an erroneous diagnosis.

DIAGNOSTIC AND TREATMENT PROBLEMS OF TARDIVE OR LATE CONGENITAL (PRENATAL) SYPHILIS

The Technic of Recognition.—The universalization of serologic testing of the child at and after birth—as part of the physical examination preceding operative procedures in childhood, as part of preschool and school health examinations, and

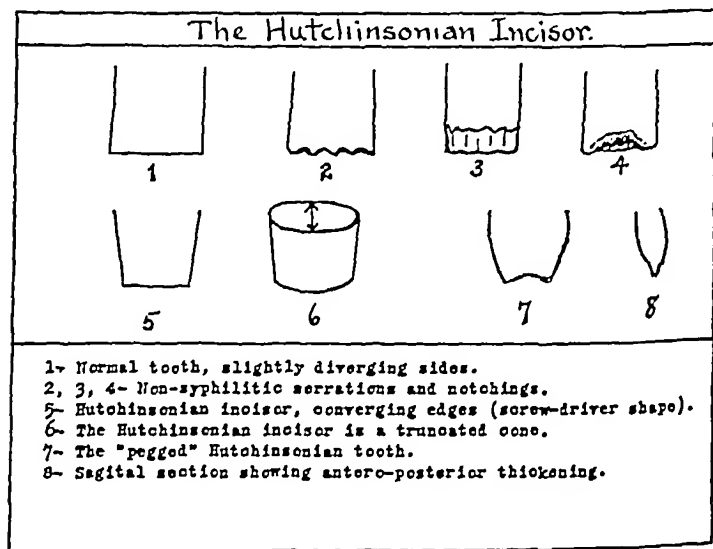


Fig. 95.—(From Stokes, "Clinical Syphilology.")

as routine features of medical examination for medical and special conditions, including particularly those of the bones and joints and of the eyes and ears—will inevitably disclose an important amount of heretofore unrecognized congenital syphilis. The estimate that from 3 to 3.5 per cent of the children in an average city population in the United States have some form of congenital syphilis may have to undergo some

revision as the non-specific positive blood test is more effectively interpreted; but the wider application of the test will very probably slightly increase rather than decrease the estimates thus far current.



Fig. 96.—Typical Hutchinsonian teeth. (Stokes, "Clinical Syphilology.")



Fig. 97.—Syphilitic upper central incisors without the notching. This patient had had interstitial keratitis, undiagnosed for years; had become almost totally deaf, and had suffered a collapse of the nasal septum, before syphilis was sufficiently suspected to lead to a blood Wassermann test and treatment. Note the rounding of the anterior face of the incisor due to anteroposterior thickening, and the "screw-driver" shape. (Stokes, "Clinical Syphilology.")

In the field of tardive prenatal syphilis, clinical acumen and the index of suspicion have a more important place than they do in the congenital syphilis of the prenatal and infant periods. Diagnostic "thrillers," and even more unhappily, "shockers," are still common occurrences in this field. The

physician who does not wish by negligence, by oversight, or by injudicious and sometimes unpardonable intervention, to injure and incapacitate a child or young person must familiarize himself with or call assistance in recognizing diagnostic signs whose mastery has been the sole property of specialists for altogether too many years. The result of the routine medical examination of the congenital syphilitic may, of course, disclose such signs as hepatomegaly and splenomegaly, with or without ascites, which attract so much attention that their clinical rarity is seldom emphasized. It is in the field of orthopedics and general surgery, in pediatrics, in otolaryngology and ophthalmology, and in child psychology, neurology and



Fig. 98.—The "mulberry" or six-year molar in heredosyphilis. Note the dwarf cusps of the anterior tooth and the hypertrophied enamel ridge which surrounds them. (Stokes, "Clinical Syphilology.")

neuropsychiatry that serious oversights and even tragic miscarriages of diagnosis and treatment occur through unfamiliarity with the commoner signs and stigmas. The cardiologist will see no congenital syphilis of the heart and blood vessels because there is none. The hematologist is seldom reminded of the existence of the disease. Diseases of metabolism and of the endocrines, so important in present day medicine, have relatively little to do with congenital syphilis as a cause.

To assist all the groups inevitably concerned, illustrations are here given of five "suspicion-arousers" and a list of stigmas which can profitably be used as blotter reminders of what to look for in everybody—for anybody may be congenitally syphilitic.

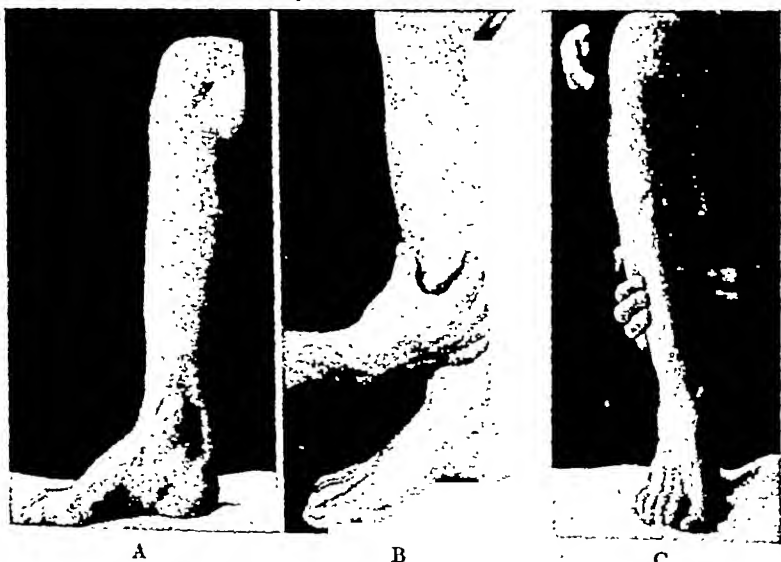


Fig. 99.—Technic of palpating the saber tibia to detect the fusiform thickening, which is quite as important as the anterior bowing. (Stokes, "Clinical Syphilology.")



Fig. 100.—A less pronounced, but nevertheless definite facies, estimated at 60 per cent. Note the look of fatigue and apathy, though the patient was well. She had a right upper central incisor, quite definitely of the syphilitic type, a negative blood Wassermann reaction, saber shins, and interstitial keratitis. Her mother had a neurosyphilis of long standing. (Stokes, "Clinical Syphilology.")

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THE LANDMARKS OF TARDIVE HEREDOSYPHILIS

Major. ¹	Secondary. ²	Minor.	Debatable.
Positive blood Wassermann. Interstitial keratitis. Hutchinsonian incisors. Mulberry molars. Eighth nerve deafness. Saber tibiae: Osteitis. Periodontitis. Simple hypertrophy. Osteitis of the nasal septum: Snuffles. Saddle bridge. Epiphysitis and osteochondritis. Splenomegaly before the fourth month. Rhagades and scars. Early dactylitis. Facies.	Frontal bosses. Aplasia of incisor teeth. Scaphoid scapula. Marked enlargement inner third of clavicles (old osteitis). Disturbance of age development ratio. Precocity and high nervous irritability. Early epitrochlear adenopathy. High narrow palatine arch.	Venous ectasia. Hypertrichosis. Ulnar deviation of middle fingers. Constitutional subnormality. Backwardness. Hypertrophic frontal suture. Craniotabes. Bilateral dacryocystitis in childhood.	Carabelli tubercle. Retromastoid adenitis. Persistent infantile hydrocele. Hypertrophic thymus and thymic abscess. Alopecia areata in children. Knock-knee elbow. Urticaria and asthma in young children. Absence of the xiphoid process.

¹ Strongly presumptive or diagnostic.

² Insufficient for diagnosis alone.

Fig. 102.—(From Stokes, "Clinical Syphilology.")

Case V. The Onset of Active Congenital Syphilitic Manifestations in the Complete Absence of Stigmas.—The case next presented to you is that of a patient observed for eight years: a young woman, age eighteen, when first seen, of great personal charm and beauty and of high position in the social world. Absolutely nothing in the family history suggests the presence of the disease. Except for a frequently recurring cervical lymphadenopathy, which might be imagined to be the beginning of the Vignolo-Luttatti syndrome of tuberculo-gummatous adenitis, her personal history was without significance.

Out of a clear sky this patient's right knee had begun to swell six weeks before the syphilologic examination, with a prodrome of five weeks of pain. Three weeks later, a painful swelling appeared on the right tibia; five weeks later the other knee had begun to swell and, coincidentally, both eyes became red, photophobia developed, and vision in the left eye became markedly impaired. The internist had insisted on serologic tests, which were strongly positive. Examination of the knees, one of which had been braced, disclosed an uncomplicated bilateral hydrarthrosis; ophthalmologic examination showed remnants of an old but previously unrecognized peripheral choroiditis and an unmistakable beginning syphilitic interstitial keratitis, with opacities and beginning corneal vascularization. The swelling and tenderness of the right tibia



Fig. 101.—Son of a mother with unrecognized syphilis, whose typical Clutton's joints had been put in casts without recognition of his congenital infection either by blood test or collateral signs. Note the unequal pupils and right Hutchinsonian incisor. (Stokes, "Clinical Syphilology.")

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was due to a recognizable periostitis, and not to the usual osteoperiosteal overgrowth of a more chronic type seen in the congenital "saber tibia." Ulnar deviation of the middle fingers, scaphoid scapulae, and some hyperextensibility of the elbow joints, all unimportant and debatable signs, were recognized.

In six months after treatment was begun vision was completely restored without residue, although slight involvement of the "other eye" had occurred; the osseous lesions had completely disappeared and the patient was, though temporarily, seronegative. Her health was again perfect and she had resumed a full schedule of activity. The total amount of treatment required to produce this result was 9 injections of arsphenamine (606); 10 injections of neoarsphenamine; 41 injections of mercury succinimide, $\frac{1}{16}$ grain each; 12 injections of potassium bismuth tartrate; and three months of potassium iodide by mouth in 90-grain doses daily. The constant attention and cooperation of the ophthalmologist was, of course, essential to the production of this literally perfect result.

It was easily apparent during the course of this treatment that a soluble, heavy metal salt, even though a mercurial, was markedly superior in its effect to a slowly absorbed oil-suspended water-insoluble bismuth salt, even though the latter was the notably effective, though somewhat painful, potassium bismuth tartrate. The patient's Kolmer Wassermann fluctuated between strongly positive and completely negative during the ensuing five years. The beginnings of a treatment nephrosis developed late, characterized by a very high output of albumin in the urine in the absence of blood cells, and disappeared during a rest period. In the fifth year, the first examination of the spinal fluid disclosed completely negative findings. The cardiovascular system was reviewed by a cardiologist, with the expected completely negative findings.

The question of marriage was then raised, permission was given, and after a year of contraceptive measures and a thorough reexamination, which disclosed nothing but a strongly positive serologic test on the blood, conception was allowed to take place. For the purpose of protecting the mother from a possible recurrence of interstitial keratitis, permission to conceive had been preceded by a course of bismuth injections, following which the previous weakly positive serologic tests were found to be strongly positive instead of negative. *Notwithstanding this fact* conception was authorized. The mother at the time of delivery had strongly positive serologic tests on the blood, and the child's cord blood was partially positive to three Wassermann technics and showed a negative Kline slide precipitation test. Blood taken on the tenth day from the child again showed a negative Kline test, but the quantity was insufficient for complement fixation procedures. Thorough examination of the placenta disclosed absolutely no evidence of syphilis.

There is hardly a point in the early diagnosis and early energetic modern treatment of tardive congenital syphilis that this case does not illustrate. Family, breeding, social position do not protect against congenital syphilis, though they often delay its diagnosis. "Water on the knee" is the familiar and sole sign of the onset of the bilateral hydrarthrosis (often also involving the elbows) which Clutton described, and which is often either the prelude to, or the presently appearing accompaniment of, interstitial keratitis. This patient did not have

saber tibiae, but instead, an acute localized periostitis. The acumen of the internist who insisted on serologic tests is noteworthy. The specific confirmation of the diagnosis was made by the prompt examination of the ophthalmologist; this is too often seriously delayed in patients outside of medical centers. The peripheral choroiditic pigmentation is of value as a confirmatory aid in diagnosis, but is by no means pathognomonic.

The circumstances under which this patient was treated made possible at the time striking comparisons between the old, and still too-frequently used inefficient, mercurial therapy of interstitial keratitis and the adequate use of the arsenicals. A case with an almost parallel history and with more marks of recognition than this one, treated by the older method, had progressed to irremediable corneal opacity and visual impairment, with ultimate glaucomatous changes in one eye. The demonstration of the value and necessity for the use of the arsenicals and of rapidly acting salts of heavy metals, illustrated en masse by the studies of Carville and Derby, and Guy and others, could hardly have been clearer. The condition in the "other eye" hardly got started before it was stopped.

The fitness of such patients for marriage, regardless of the serologic findings, and the presence of a transient, transmitted positive serologic test in the infant from the seropositive mother, with ultimate disappearance of the infant's positive serology and subsequent complete good health, are all well borne out. That pregnancy, along with many unaccountable and even unrecognized influences, may provoke revivals of interstitial keratitis constitutes practically the only fear for this young woman's future health and happiness. Third generation familial syphilis exists, but authentic reported cases are exceedingly rare and constitute no grounds for withholding the marital privilege from an adequately treated congenitally syphilitic person.

A case thus diagnosed and managed of course provides no illustration of the occasionally encountered high resistiveness of congenital syphilis, and particularly of interstitial keratitis, to even modern arsenical-heavy metal therapy. There are elements of the unaccountable in the behavior of interstitial keratitis which, of course, cannot be reconciled with the conception of a local spirochete-produced lesion responsive to anti-

spirochetal therapy. The patient here presented was treated before the days of non-specific emphasis in the treatment of syphilis. Today, refractory interstitial keratitis, resistant osseous manifestations, and neurosyphilis in the congenitally syphilitic person are all effectively treated by pyrexial methods, and most effectively by malarial inoculations. While congenital syphilis of the heart and great vessels is a rarity of the first order, some question has been raised in the minds of observers who follow congenitally syphilitic patients that have received malarial therapy, as to whether or not the fever induced by infection methods may not leave some myocardial impairment in its wake. This question, as time elapses, will deserve painstaking special study. (See Case VII.)

Case VI. The Serologic "Pick-Up" in Routine Examination, and Congenital Syphilis.—This next case to be presented to you is that of a young man in splendid health who had repeatedly passed without adverse findings the physical examinations of a government service. When tonsillectomy was advised, routine serologic tests on the blood were taken, and to the astonishment of all concerned were returned as strongly positive. Called in consultation on the matter, the syphilologist confirmed the strongly positive serologic test but could find no anamnestic or clinical evidence of an acquired infection. The physical examination disclosed a human specimen of such obvious physical fitness that the inclination would be to give him the "once-over" with a pat on the back and a passing grade. Under such circumstances it has been our practice to redouble our attention to possible obscure evidences of prenatal syphilitic infection. As a result, in this case, a liver two finger-breadths below the costal margin on ordinary examination was identified by three observers, the enlargement being even more apparent on the Middleton maneuver. The syphilologist rated the facies at 25 to 35 per cent of a diagnosis. The upper central incisors were indeed remarkable in that they appeared to present accessory cusps suggesting almost Carabelli tubercles, though the latter are probably without diagnostic significance for congenital syphilis. Very fortunately the six-year molars, which rapidly become carious in many of these patients, were still retained in the lower jaw. That on the left particularly showed a marked hypertrophic enamel edge, and the grinding surface of the tooth at the site ordinarily occupied by the four abortive cusps of the Moon molar were exactly replaced by a four leaf clover pattern filling—the shadow, so to speak, of the dystrophic "mulberry" or Moon six-year molar of congenital syphilis.

On the basis of these findings the syphilologist reported to the referring agency that he believed the patient to have congenital syphilis and advised the latter to conduct further tactful inquiry into his family history through his home physician and others. The result was indeed revealing. The family physician had recognized the patient's congenital syphilis in infancy, and had treated him for it with mercury by mouth and inunctions. The mother of the patient was a tabetic with advanced symptoms and signs. One sibling had had his vision seriously impaired by interstitial keratitis and showed other typical stigmas. Apparently through the reticence of those aware of the situa-

tion and through the methods of treatment then in vogue syphilis had literally wrought havoc in this family in one direction, leaving only the most insignificant traces in another.

A number of examples of this type of situation will unquestionably be turned up by the popularization of serologic surveys, by law or otherwise, throughout this country. The treatment advised and carried out and the ultimate future of the case might well be a lesson to industrial and other agencies disposed to cancel out and discharge as industrially unfit and disabled individuals of the type of this young man. Through the intelligence of the interested Government authority, the patient's position and promotional rating remained unchanged. He received a total of 3 neoarsphenamine injections, 12 inunctions, 8 injections of mercury salicylate, and 35 injections of bismuth subsalicylate without reaction. His eye grounds were found to be perfectly normal, his spinal fluid likewise. Permission to marry was given, and when last seen, still strongly seropositive, the patient was nonetheless the husband of a healthy woman and the father of a healthy child. All treatment has been suspended regardless of the serologic fixed positives. For those who may question the significance of the liver in relation to the picture as a whole, it may be stated that it had completely receded and was no longer palpable following the first six months of treatment.

Case VII. Tardive Congenital Neurosyphilis—Diagnosis and Treatment.—The last case to be presented to you is that of a young man of twenty-two whose accurate history and treatment cover a period of eighteen years. A premature child at eight months, born of parents who had been seronegative on the blood nine years before, without a history of infection or treatment but with one preceding miscarriage, this baby had developed an eruption of the palms, soles and face which was called "eczema" even with snuffles present. No tests were made, no systemic treatment given. At three years of age, a pediatrician was called to see another eruption on the face, palms and soles, and a dermatosyphilologist secured positive serologic tests for syphilis on the child's blood.

The subsequent treatment consisted of 6 to 8 intramuscular injections of neoarsphenamine, 15 to 17 mercury inunctions yearly for nine years, and 15 to 25 grains of potassium iodide three times daily at the time of the inunctions only. An examination of this child's spinal fluid was first made when he was eight years old and was reported "positive." Two Swift-Ellis treatments were given, the fluid still being positive on the second occasion. A year later a lumbar puncture was said to be negative. The child started school at eight; he made fair progress at first but then steadily fell behind. At the time of the syphilologist's examination the child was an obvious imbecile, to judge by

his conduct and cooperation. The physical examination disclosed a suggestive facies, a Moon molar, and unequal pupils reacting very sluggishly to light. The deep reflexes were present, sensory changes could not be satisfactorily interpreted, and there was no evidence of pyramidal tract or lateral column involvement. As an afterthought, the tibiae were rated as showing fusiform thickening. The serologic tests on the child's blood (Kolmer, Kahn, Kline and Hinton) were strongly positive—those on the mother's blood being likewise. The child's spinal fluid showed 37 cells, Kolmer-Wassermann 444. Pandy strongly positive, colloidal mastic 4555543111.

Obviously the serologic and clinical diagnosis at age twelve in this case was congenital syphilis and juvenile paresis. The choice of treatment rested, to all practical purposes, between tryparsamide and malaria. Some hesitation was felt about using tryparsamide in so uncooperative an individual, who could not give an adequate report of his eye symptoms to protect him from toxic amblyopia. An additional opinion as to the value of malaria in such cases at that stage of our knowledge was essentially adverse.

Accordingly, the boy was placed on tryparsamide therapy, reaching a dose of 1.5 Gm. per weekly injection by the fourth treatment. Fortunately no eye complications developed. The change which took place in the child's mentality (he was attending a school for subnormal children) in the course of three months was remarkable. As one often observes in these cases, he showed a type of "island" preservation of mental alertness, possibly associated with regional localization, activity or inactivity of the parenchymatous process. While not particularly improving in certain assigned tasks, he showed a remarkable increase in reasoning power and acuteness of observation. The speech defect remained a pronounced and persistent symptom. Memory definitely improved. There was a steady weight gain, amounting at times to as much as a pound a week.

By the thirtieth tryparsamide injection, which with the summer interlude constituted the first course of the second year of treatment, sexual maturity had begun and the advance in alertness was marked. Even through the continued therapeutic improvement, the well-known disposition of paresis towards exacerbation and remission could be recognized. Remissions often coincided with periods of discontinuance of treatment, as during the summer months when the outdoor life and sunlight undoubtedly affected the child favorably. By

the beginning of the third year of treatment (88th tryparsamide injection) the patient came regularly, unescorted, for treatment, and conversed in animated and intelligent fashion at times and with dullness and hebetude at others. Some of his political commentaries and his remarks on industrial processes and relations were of astonishing penetration.

Note now that despite all the symptomatic improvement the patient's serologic tests remain virtually unchanged: blood strongly positive, spinal fluid 18 cells, Kolmer Wassermann 444, Pandy 4 plus, and colloidal mastic 5555310000.

As a rest from the arsenical the patient was given bismuth followed by thirty more injections of tryparsamide. It was then decided that, in view of the unchanged spinal fluid findings, he should receive a malarial course (he was fifteen at the time); he sustained very satisfactorily a siege of twelve chills. Immediately following this treatment the impression of mental set-back was strong. Tryparsamide was then resumed in 2 Gm. doses weekly, and following thirty more injections, further notable mental progress had been made.

Note now that following the malarial siege plus tryparsamide the spinal fluid and blood. abnormal despite more than 100 tryparsamide injections, had become completely normal; the Kolmer, Kline and Kahn tests were negative, the spinal fluid Kolmer-Wassermann was 0000 (one cell), and the colloidal mastic 1110000000; globulin was normal. This precisely fulfills the observation of Solomon with regard to the rapid response of seroresistant patients to malarial therapy after prolonged tryparsamide preparation.

Among the interesting symptomatic remnants should be noted again the persistence of the speech defect, which was such that the patient could hardly be understood at times, and the blank or expressionless facies with flattening of the nasolabial folds. Again, during the subsequent months of tryparsamide therapy there was evident independence of the now normal serologic findings and the ups and downs of the parietic mental picture during the course of the disease. In the fall of 1935, advice to the school to emphasize certain features in the boy's training, especially his defective speech, produced striking results—an excellent illustration among many in this case of the great importance of the help of skilled, child

training experts accustomed to dealing with impaired mentality. While part of the subsequent and still more remarkable gain is undoubtedly to be attributed to the persistence of treatment, the importance of training in dealing with special defects cannot be overemphasized.

At this time, with counsel from the neuropsychiatrist (Solomon) who had carried through the malarial therapy, tryparsamide was reduced to one monthly injection. Thereupon the boy progressed mentally and physically even more rapidly and definitely than before. He remained serologically negative on the blood, and sustained a thorough-going cardiovascular examination by Wolferth with negative results except for a tendency to tachycardia, which led to a reduction of his athletic activities. Immediately following this, the patient underwent psychological classification by a variety of intelligence tests. These resulted in a grading and predictions for the patient's future so astonishingly pessimistic that those who had had continuous contact with him for the preceding five years simply could not accept them.

In the ensuing half-decade from 1934 to the present time, the patient has been continuously under observation by the syphilologist and has received twelve tryparsamide injections per year. The spinal fluid has twice been completely negative, and the blood likewise. Under the direction of an unusually good school he has made continuous progress and certainly can no longer be rated as a low-grade imbecile, from the standpoint of his placement in the world at large. He conducts a good conversation in reasonably distinct speech, shows intelligence in general, personal and special affairs, and has improved greatly in physical coordinative power and accuracy of performance. That he can ever assume full-fledged adult responsibility for himself may properly be doubted, but his placement in farm life, for example, would be entirely possible, and the comfort he has been to his family is immeasurable. That he gets "jittery" when put to the test before strangers is of course a serious incapacity and a probable explanation of his low grading in intelligence tests.

What moral shall we draw from a tale like this? Serologic testing routinely during pregnancy would probably have done away with most of the telling. Action by the physician who

made the incorrect diagnosis of eczema would have done still more. A spinal fluid examination, complete and accurate on all counts, performed within the second or third year of life and preferably within a short time after the serologic recognition of the infection in the first year, would almost certainly have saved this boy, because the response of children to even moderate treatment for the disease, of a standard type, leads to better results for the nervous system than are obtainable in adults. With the chronology of the case in hand, there can be little excuse for the desultory and inadequate treatment that followed the recognition of the child's neurosyphilis. It was no doubt a part of the traditional pessimism of the day, from which we have not yet recovered. Early recognition and determined and intensive treatment with tryparsamide and fever for the congenitally neurosyphilitic, and particularly the preparetic or juvenile parietic child will unquestionably lead to therapeutic results and a saving of life and intelligence comparable to that now obtained in the management of the adult form of the disease. In the rescuing of as much of the child intelligence impaired by neurosyphilis as possible, the help of special skill and school facilities for the impaired mind is as essential as ophthalmologic cooperation in the care of interstitial keratitis.

SUMMARY

There have been presented before you seven cases of congenital syphilis, illustrating the following topics:

1. *The mother who acquires syphilis and becomes seropositive during her pregnancy.*—The average prenatal examination law requiring blood serologic testing at the time of the first prenatal visit cannot control such a problem, which, in actuality, requires subsequent study in late pregnancy and at the time of delivery. Fortunately this problem is not common except in obstetrical practices involving unmarried mothers or sexually promiscuous women, but the medical profession as a whole must be constantly aware of this stumbling block in the control of congenital syphilis because of the importance of the public health problems involved.

2. *The seronegative syphilitic mother.*—No pregnant woman can be assured the birth of a healthy child unless she has received some prenatal therapy during each pregnancy.

The mere fact that a woman is pregnant, however, and that the time for administering protective prenatal therapy is growing shorter as the pregnancy progresses, is no reason for commencing treatment for syphilis on what would be considered inadequate evidence for establishing the presence of this disease.

3. The problem of the *seropositive non-syphilitic baby* has been largely solved with the application of the quantitative titred Wassermann. Where this laboratory procedure is not yet available, dependence on the standard technics performed in a good laboratory is satisfactory. The syphilitic reagin transferred from the maternal blood stream is only infrequently detectable in the infant after the third week of life.

4. The *roentgenogram of the long bones of the newborn infant* is sometimes helpful in solving the diagnostic problem during the first few weeks of life when serologic testing is not wholly dependable, provided, however, the presence of the disease is not deduced from minor or equivocal skeletal changes.

5. The healthy, adult, congenitally syphilitic woman practically devoid of stigmas, with an apparently negative family history and a social position above the average, may without warning develop interstitial keratitis, often with concomitant Clutton's joints (bilateral hydrarthrosis). Under thoroughgoing combined treatment with the arsenicals and soluble heavy metal intramuscularly, including mercury if bismuth seems slow in action, she can achieve a practically symptomless and residue-free recovery, with subsequent fitness for marriage, regardless of positive blood serology and give birth to a healthy child temporarily seropositive on the cord blood.

6. Persons found seropositive as part of a routine physical examination or other routine testing practice should be carefully searched for the more unfamiliar stigmas of prenatal syphilis, including in this a thorough-going inquiry into the family history. After adequate treatment as for a seropositive latent acquired infection, such persons may marry regardless of their serology and become the parents of healthy children. There is no excuse for any discrimination against them in any legal, professional, economic, or industrial field.

A number of such individuals will undoubtedly be identified in the now prevalent serologic survey.

7. Congenitally syphilitic individuals with neurosyphilis, and even typical juvenile paresis, have an excellent outlook under tryparsamide and malaria in modern treatment. Spinal fluid examination within the first two years of life with positive findings, adequately dealt with, will forestall slumps in conduct, deteriorative changes, pseudo-imbecility and ultimate death or disintegration in the large proportion of cases. The assistance of skillful school and personal training by experts is invaluable.

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THE TREATMENT OF ASTHMA

It was with serious misgivings that the writer consented to prepare a clinic on the subject of the treatment of asthma. In the first place, the subject is so large that it cannot possibly be covered completely in the space available. The matter is further complicated by the fact that details of procedure cannot be set down in the form of a routine to be followed in every patient. The physician does not treat asthma but a patient with a symptom which may be due to several or many of hundreds of possible causes, and with an increasing range of complications, the longer the disease lasts. There are few conditions in medical practice in which treatment must be so highly individualized. Moreover, it might be argued that the proper treatment of asthma belongs in the province of the specialist, since only the specialist can be expected to be adequately equipped, not simply in experience but especially in diagnostic and therapeutic materials. And finally, to write an article on only the treatment of a disease in which correct and detailed diagnosis is so essential, is like telling only the last half of a story.

And yet for a number of reasons it is important to bring the principles of the treatment of asthma to the attention of the general practitioner and the internist. Practically all patients with asthma are first seen by them, and most asthmatics, even after consultation with an allergist, continue their treatment in the hands of the general practitioner. That which in the future may well prove to be a most important matter, the *prophylaxis* of asthma, lies primarily in the province of the general medical advisor. Moreover, he is less likely to make the mistake of considering only the asthma and failing to see the patient as a whole.

Conversely, the practitioner must realize his own limitations as regards the detailed management of asthmatics. Next to incomplete diagnosis, incomplete treatment is the most important cause of therapeutic failure in asthma. The incompleteness of the treatment is usually to be laid at the door of the practitioner who fails to carry out in its entirety the advice of the consulting allergist. Let not the practitioner fall into the error of looking on the allergist as a mere skin-tester or glorified technician (nor should the allergist allow himself to be one!).

Therefore a clinic on the treatment of asthma is fully justified: granted that it cannot go into every detail, but serves rather to emphasize the high spots, warn against the commoner pit-falls, and point out some recent and useful advances. As for the matter of starting a story in the middle, every installment of a serial story in a literary magazine begins with a brief synopsis of what has gone before: why deny the medical writer the same privilege? And so, a few words on:

THE DIAGNOSIS OF ASTHMA

While in many diseases the establishment of a nosological diagnosis is enough to plan the entire treatment, in asthma this is only the first of many diagnostic steps that must precede a complete treatment. Having decided that the patient has asthma, and not one of a variety of other causes of dyspnea, we must find out:

1. *All* the things to which he is sensitive, be they things he eats, or that he inhales in his home or elsewhere, at his work or play.

2. All complications which may have arisen in his respiratory tract: sinus infection, nasal polyps, bronchial infection, bronchiectasis, bronchostenosis, emphysema.

3. All other factors, involving pathologic anatomy (*e.g.*, marked deflection of the nasal septum with firm septoturbinal contact), or pathologic functional disturbance (*e.g.*, hypertension), or unfavorable psychologic situation (such as social maladjustment): factors any one of which may be the straw which breaks the sickly asthmatic camel's back.

To arrive at such a *complete diagnosis* requires:

1. The most searching *history*.

2. *A physical examination*, which in addition to the usual routine must always include an examination of the upper respiratory tract by a rhinologist, using the nasopharyngoscope and transillumination of the sinuses. In selected cases bronchoscopy is indicated.

3. *Laboratory studies*, in addition to a blood count, urine analysis and Wassermann test, should include x-rays, usually of the sinuses, often also of the chest, and in some instances of the bronchial tree after lipoidol instillation.

4. *Complete skin tests*: not in the routine of a technician, but by some one who knows what to test for and how to interpret the results.

5. In all cases *treatment itself is diagnostically important*, for it not only determines the significance of test results, but may serve to discover causes which tests failed to find.

6. Nor is such a complete diagnostic survey necessarily the last diagnostic study. The fundamental trouble with the allergic patient is not that he has asthma, or that he is sensitive to feathers, but that he has inherited the ability to become sensitized more easily to things in his environment than do normal individuals. Therefore the allergic's sensitization pattern is not a fixed and final thing: in the course of the years old sensitivities disappear and new ones can develop, a possibility among those to be considered if the patient suffers a relapse.

TREATMENT OF ASTHMA

The subject will be discussed from the standpoints of, first, the general principles which underlie all phases of the treatment of asthma, and second, the application of these therapeutic principles to the individual case.

GENERAL PRINCIPLES

Since sensitivity is, in the present state of our knowledge, the first cause of asthma, treatment must be directed first, last and all the time to the:

I. **Allergic Factors.**—The first axiom in allergy is that:

(a) *Avoidance* of that to which the patient is sensitive gives by far the best therapeutic results. If the patient is sensitive only to external substances, *i.e.*, things outside of his own body, and no secondary infectious complications are pres-

ent, then the complete avoidance of those substances will give complete relief.

The avoidance of dietary factors, while it may appear simple enough at first glance, is nevertheless beset with a surprising number of difficulties and pit-falls. The first step in the direction of avoiding food allergens is a diet based on a list of foods which gave unequivocally negative skin tests. This means that the patient must eat no food which gave even a weak or trifling skin reaction. It also means that he should eat no food which was not tested. It means further, in view of the fallibility of food tests, that the patient should avoid any food which experience has shown to be harmful, irrespective of the skin test result. And the avoidance of the forbidden foods must be *complete*. Yet failure to make the avoidance complete is encountered in the first weeks or months of nearly every patient's experience.

Why is there difficulty in making avoidance complete? Because patients—and most physicians—avoid the obvious but fail to avoid the hidden ingredients of foods. How many patients know the scores of guises under which egg, milk and wheat masquerade? Or that sardines are commonly boiled in peanut oil before packing? Or that ice cream powders contain Karaya gum? Or what is in baking powder or Worcestershire sauce? Or from what flowers the bees collect their honey? The allergic's guiding rule should be: *If you don't know what's in it, don't eat it.*

Fortunately there are now available for patients a number of manuals in which adequate information on food constituents may be found. Since the results of treatment must so largely depend on the intelligent co-operation of the patient, his instruction becomes a prime duty of the physician. A manual will prove most helpful in this direction.

The avoidance of inhaled factors is always possible, but at times highly impracticable. Yet the therapeutic success of avoidance, with inhalants as with foods, depends wholly on its completeness.

Pollen can be completely avoided only by going where the offending pollen does not exist (also at sea) or by an uninterrupted stay in a room supplied with filtered air. The latter expedient is one which every hospital should be equipped to

provide, not only for asthmatics, but for hay fever sufferers who must be subjected to laparotomy in the pollen season. In an emergency, a pollen-free atmosphere is well approximated in an oxygen tent.

Animal epidermal substances come in for serious consideration, especially in the home. We spend a third of our lives in our bedrooms, more time than in any other place. There can therefore be no compromise in the matter of complete avoidance of offending substances in the bedroom. Yet how often does the room-mate continue to sleep on feathers, or the asthma recur when the first cold night calls out the down quilt? A common current fallacy is that covering a pillow or a mattress with a so-called impervious cover insures complete avoidance: it certainly does not! It materially reduces the intensity of exposure and so is useful to prevent sensitization to bedding materials in allergic individuals not yet sensitized, or as a temporary measure for the sensitive, to be used while traveling. But in the sensitive patient's bedroom such offending substances should be completely removed.

Patients who are not relieved by removing feathers, horse hair, wool, etc., from the bedroom may find it necessary to extend the elimination to all parts of the house, with special attention to all bedding, upholstery and rugs. Nor should one forget the felt pads, made of the matted hair of various animals, and commonly used under rugs and carpets.

Simply to banish the family cat will not rid the household of the years' accumulation of cat hair, nor does it prevent contact with cat hair in furs or the lining of gloves or slippers.

Specific organic dusts of many kinds offer similar problems. Some are common offenders in the household. Many asthmatics, especially those with the usual pollen sensitivities, are sensitive to pyrethrum pollen, the active ingredient of many insecticides. If the patient is sensitive to orris root, then all members of the household should use orris-free cosmetics. An increasing number of specific dust sensitivities are being found in connection with occupations. Complete avoidance may then at times be achieved only by a change of occupation. Or it may be necessary for an individual to change clothing at his place of work, so as not to bring home the offending dust to a sensitive asthmatic.

Avoidance of house dust by those sensitive to it is a common and a vexing problem. *Complete permanent avoidance* may at times be achieved by a change of residence, a change which may be made imperative if the offending dust component is the mold spores from a damp cellar. Only too often, however, the source of trouble lies in the house furnishings which, if not discovered, will continue to plague the patient when they go with him to his new environment. *Complete temporary avoidance* of house dust is often possible (and necessitated as an emergency therapeutic measure) by removing the patient to a hospital. The prompt relief which a patient experiences upon hospitalization and the equally prompt recurrence of trouble when he goes home are the best possible evidence of the localization of the causative agent in his own home, and that is most often his own house dust.

(b) *When complete avoidance of allergens is impossible or impracticable*, two measures become necessary. The second is obvious to all: desensitization. Equally important, but often overlooked by those not trained in allergy, and therefore in the interest of emphasis to be considered first, is:

1. *Partial Avoidance*.—In a large measure the production of symptoms by an allergen in a sensitive patient is a quantitative matter. A very little of the allergen may cause no symptoms at all. More allergen will produce mild symptoms and much allergen provokes serious trouble. Desensitization is rarely, if ever, complete—the better term is “hyposensitization”—and consequently will fail to protect a patient against huge amounts of the allergen. Consequently, the more of the allergen which the patient manages to avoid, the more likely will desensitization prove effective against the remaining allergen. In short, partial avoidance is usually vital to the success of desensitization treatment.

Pollens may be partly avoided by such expedients as an air filter in the bedroom or office, or by keeping bedroom windows closed by day and by using an impervious bed spread (rubberized sheet, paper) to keep pollen off the pillow by day, and by spending the vacation at the seashore or in the deep woods instead of the country.

Animal epidermal substances and other materials used in bedding, such as cotton or kapok, can and should be partly

avoided by the use of impervious pillow and mattress covers when the patient is traveling. By covering woolen blankets with one or two layers of cotton sheeting the wool dust contact is much reduced. This objective is also helped by using old blankets, of dyed wool and repeatedly washed, so that they shed very little, and by avoiding new fuzzy soft-woven blankets of native white wool.

Occupational dusts may be partly avoided by suitable dust-removing devices in the work-room and by the use of masks.

Every effort should be made to avoid as much *house dust* as possible: painted walls, rather than wall paper; certainly never oatmeal-finish wall papers or burlap wall coverings; bare floors, or with linoleum or small washable cotton rag rugs; as little as possible in the line of hangings, and these of the lightest and least offensive materials; plain furniture with a minimum of upholstery; no heating or ventilating devices that involve recirculation of air from one part of the house to another; no animal pets; and no insecticides that contain pyrethrum. Especially in the bedroom should these measures be carried out to the acme of monastic simplicity. The bedroom door should always be closed to keep out dust from the rest of the house. The patient should also avoid visiting other houses in which he has experienced trouble.

2. *Desensitisation* becomes necessary when complete avoidance is impractical and partial avoidance does not relieve. This is undertaken by the subcutaneous injection of increasing amounts of the specific extract, in case of foods also by the feeding of increasing quantities, beginning with amounts too small to provoke symptoms, and aiming at a maximal dose comparable in amount to that met with in ordinary exposure. The commonest examples are treatment with pollen extracts and house dust extracts. In addition to these, orris root, feathers, hair and an occasional occupational dust are used in the small minority of patients who for unusual reasons find it impossible to achieve adequate avoidance of these substances. Food desensitization needs to be attempted only with those hardest to avoid: egg, milk and wheat.

Although space does not permit a detailed description of desensitization technic, it will be well to point out certain important principles, the neglect of which will lead to failure:

Use the Proper Extract.—This seems obvious enough. In case of pollinosis one should use all the pollens which are responsible for symptoms. In case of house dust, use an extract prepared from the dust of the patient's own house.

Begin with a Small Enough Dose.—Thus with pollens start with that dilution which just fails to give a reaction on end-dermal testing.

Do not Give Injections too Close Together.—While it may be necessary to give pollen doses every day to those reporting late for treatment, there is far less chance of an unfavorable reaction and the end result is always better if the doses are spaced at four- to seven-day intervals. The latter interval is best with anything except pollens.

Do not Increase the Dose too Rapidly.—The proper increment must be learned from experience with the extract and with the patient.

In Case of Reaction, do not Increase the Next Dose.—If the reaction was not severe, repeat the same dose. If a reaction again occurs, or if the first reaction was severe, reduce the dose and later proceed more cautiously.

When Symptomatic Relief is Achieved, Level off the Dosage.—This is especially the case with house dust extract. After a few doses at the regular interval, the interval may be prolonged by a day each time, so long as the patient does well.

Perennial treatment in pollinosis should be given if pre-seasonal treatment alone does not give complete relief, or if the patient finds it more convenient.

Desensitization by feeding egg, milk, or wheat is subject to the same general principles, except that feedings are given daily, using the well-cooked, at times diluted, food instead of an extract. When adequate tolerance is attained (it takes from six months to two years), some of the food must be eaten daily to hold the tolerance.

So-called nonspecific desensitization with peptone, histamine and other protein derivatives has rarely proved successful in asthma. (The results have been somewhat better in certain other allergies, such as urticaria.)

Physical Allergy.—In patients who have had asthma for a long time, the reflex processes involved in the asthmatic paroxysm, by reason of frequent repetition, may in time be called

forth by less and less of a specific stimulus, or by less specific stimulus plus some nonspecific stimulus. Physical agents, notably temperature changes, and especially cold, may be the nonspecific stimulus that precipitates an attack. In occasional patients the physical agent alone may finally be able to provoke an attack, giving rise to the term "physical allergy." The mechanism of such attacks suggests that of a conditioned reflex.

All asthmatics should avoid rapid temperature changes. In the winter the bedroom window is not to be opened more than an inch, so that the temperature in the bedroom does not fall below 60° F. The patient must avoid cold drinks or ice cream with the evening meal or at night.

Over-filling the stomach, especially late in the day, can also be such a nonspecific cause in bringing on symptoms. The asthmatic is therefore better off if he eats four smaller meals, with the chief meal in the middle of the day.

It is probable that psychic stimuli may at times act in a similar way. The implications are obvious.

II. The Treatment of Complications.—This involves not only those resulting from asthma itself, but any co-existing disease the patient may have. First to be considered are:

(a) *Nasal Complications.*—The commonest abnormality is a:

(1) *Deflected Septum.*—A crooked septum or a septal spur should be corrected if there is firm lateral contact with the turbinates, because such a defect carries the triple threat of interference with breathing, interference with normal sinus drainage, and of reflex influence on bronchospasm. *The operation should never be performed, however, during the pollen season, but preferably after October 15 and before April 1, lest the patient develop a new pollen sensitivity.*

(2) *Nasal polyps*, if large enough completely to obstruct, should be removed, the larger ones irrespective of the season. Then a thorough program along allergic lines should be carried out. At the end of six to eight weeks it will be found that there has occurred a certain amount of regression in the polypoid change, even at times to the extent of disappearance of the polyps. Polypoid tissue which remains after two months of treatment directed against allergic factors should then be

thoroughly removed, but not during the pollen season. Allergic measures must be continued after the removal of the polyps, not only because of the asthma, but to prevent the recurrence of the polyps.

(3) *Sinus disease* calls for treatment along the same lines as mucous polyps, and in addition necessitates the treatment of infection. Allergic management for two months, together with the use twice daily in most cases of a mild shrinking nasal spray [*e.g.*, cocaine hydrochloride gr. v, ephedrine sulfate gr. x, epinephrine (1:1000) ℥xx, antipyrin gr. vi, water to make ʒiii] will result in some lessening of the mucosal swelling, better drainage of the sinuses and consequent improvement of the sinus disease. What remains after two months will require surgical treatment.

The guiding principles in sinus surgery in allergics are: (1) Thorough, so-called radical measures (*e.g.*, Caldwell-Luc operation on the antrum) are in the long run the most effective and therefore the most conservative. (2) More than the usual care in after-treatment is required to guard against synechiae. (3) Operation should be carried out in a pollen-free season. (4) Do not do too much at a single sitting (*e.g.*, a bilateral Caldwell-Luc).

The treatment of the infection in the sinuses is along the lines to be discussed under bronchial infection.

(b) *Bronchial Complications*.—These include, first, and present in a majority of patients, bronchial infection. In a few cases there also occur bronchiectasis and bronchial stricture.

The treatment of infection, whether it be in the sinuses or bronchi, is an extremely important part of the management of asthmatics. Unfortunately it is very often mismanaged, because the physician commonly treats the condition according to the usual principles of drainage and immunization and forgets to reckon with the allergic nature of his patient. Bacterial allergy is a very common factor in asthmatics. Its behavior is very different from that of other forms of allergy in a number of ways: its intensity varies widely; its local manifestations (edema, hyperplastic swelling of mucosa) are more chronic (although occasionally they are dramatically acute), and are hopelessly intermingled with the ordinary processes of

infection; its presence cannot be determined with any degree of certainty by skin tests. *But its possible presence must not be ignored.* I have seen a number of attacks of status asthmaticus precipitated by unwise vaccine dosage (*in fact, I am becoming convinced that status asthmaticus is chiefly a matter of bacterial allergy*), and I know of one death that occurred a few minutes after an initial vaccine injection of 10 million organisms.

As in all localized infections, *adequate drainage* is a first requirement. In the nose, this involves the use of shrinking sprays to open sinus ostia, local rhinologic treatment and surgical drainage. In the bronchi, it means keeping the sputum thin by the use of expectorants (iodides are most helpful), and the use of gravity (postural drainage 10 to 15 minutes several times a day, especially at bed time). Local treatment through the bronchoscope may prove very helpful.

At this point *bronchoscopy in asthma* deserves a paragraph. Skillfully performed, under local anesthesia only, bronchoscopy is a valuable help in diagnosis and treatment that is far too rarely used. Any asthmatic with a chronic cough that has lasted for several months deserves bronchoscopy, unless there are definite contraindications (aneurysm, serious cardiac disease, advanced senility). In no other way can one diagnose stricture of a bronchus. It is the best way to get an uncontaminated sputum specimen for culture and vaccine. It is the best way to diagnose bronchiectasis, both by direct inspection and bronchography. Iodized oil (having ruled out iodism and sensitivity to the oil in question) should be instilled into the part of the bronchial tree under investigation *through the bronchoscope*: it is the only way one can be sure the oil will get into the right place. The oil can also be quickly and safely removed through the bronchoscope. In many cases the mere passage of the bronchoscope seems to have a beneficial effect, much as the passage of a sound may set aside urethral spasm.

Vaccine therapy is exceedingly helpful in dealing with infection in sinuses or bronchi. If there is purulent sputum or if material is obtained at operation from the interior of a sinus, an *autogenous vaccine* is best. Not infrequently a specimen obtained through the bronchoscope yields only a single species of organism on culture. In case several different organisms

are obtained, all are incorporated in the final vaccine, with proportionately greater amounts of the streptococci, *H. influenzae*, and hemolytic staphylococci. A good rule is to use the approximate proportions found in a stained smear of the fresh material. Attempts to pick the organisms on the basis of reactions they produce in the patient's skin have not proved satisfactory.

Great care should be taken in determining the initial dose. In no case should this be larger than 2 million organisms (an endermal injection of 0.02 cc. of a suspension containing 100 million organisms per cc.). If the patient's cough and wheezing become worse during the next twenty-four hours, the subsequent dose should be reduced to one-tenth of the first dose by preparing a new dilution containing 10 million organisms per cc. In patients who have ever been in status asthmaticus, or in elderly asthmatics with long years of chronic cough and bronchitis, it is wise never to begin with a larger dose than 200,000 organisms, and in one patient I have had to reduce the dose to as low as 20,000.

In the patients who suffer these severe reactions, serious damage is often done by physicians who persist in using larger doses and in increasing the dosage in spite of reactions. Then both patient and doctor are convinced that the vaccine is harmful rather than helpful and the vaccine is thrown away. Yet in these very cases proper vaccine therapy gives its best results: the fact that even tiny doses cause reactions proves that the vaccine contains an important allergen and so should be the thing with which to desensitize the patient. It should be used in small enough dosage for exactly the same reason that determines the dosage in pollen therapy: the avoidance of general reactions.

The *frequency* of vaccine doses should not be more than once a week. Injections after the first should be given subcutaneously on the outer aspect of the upper arm with a tuberculin syringe that has been sterilized by boiling. The dosage as a rule may be increased from an initial of 2 million to 5 million, then 10, 20, 30, 40 million and so on to 100 million; then weekly increases of from 50 to 200 million, depending on local or general reactions. In some patients there is reached a "ceiling dose," beyond which any increase causes

trouble. That dose, or one slightly smaller, should then be continued once a week.

When the vaccine is used up—the initial supply is good for a year—a new vaccine should be prepared. If the patient now no longer has purulent nasal or bronchial secretion, then a so-called *stock cold vaccine* is employed. In all asthmatics who give a history of recurrent winter colds, such stock vaccine treatment has an excellent prophylactic value, in that they get over their colds in a few days without complications instead of suffering for weeks thereafter with a purulent bronchitis. Such treatment is best begun in late summer and continued at weekly intervals well into the winter. The chief precaution has again to do with the dosage: a small initial dose of a 10 per cent dilution of the stock material. *Never give the usual dosage recommended on the label.*

A third measure, which when feasible is very useful to combat infection, is a *change of climate* during the winter months. The mildly stimulating climate of the western parts of the Carolinas or of northern Georgia is preferable to the enervating heat of the Florida coast. But few patients are able to meet the most important condition: to leave the North in late December and not return before the first of May.

[There is more to follow on the subject of climate and asthmatics.]

Bronchiectasis is a comparatively rare complication of asthma. This statement is based on our experience in hundreds of observations by bronchoscopy and bronchography. (Beware of an x-ray diagnosis without the use of a contrast medium!) It usually occurs in the form of localized bronchiectasis in larger bronchi. Its treatment is essentially that of infection as above described, together with local treatment through the bronchoscope.

Bronchial stricture, a rare complication usually found on bronchoscopy in a large bronchus and apparently a late result of infection and ulceration, should be suspected when physical signs persistently predominate in one lung area. Its diagnosis and treatment (systematic dilatation) belong to the bronchoscopist.

(c) *Pulmonary Emphysema*.—This is a common and distressing complication of late asthma and it offers little chance

for therapy. In addition to the treatment of the allergic and infectious factors, one can at times improve the efficiency of diaphragmatic breathing by the use of an abdominal belt that pushes abdominal viscera and diaphragm higher into the thorax. Regular exercises, designed to increase respiratory excursions, especially the expiratory phase, are of value to all asthmatics, including those with emphysema.

(d) *Other diseases*, whether pulmonary, such as tuberculosis, or extra-pulmonary, such as diabetes, are to be treated in the usual way; but at the same time one should not lose sight of every phase of asthma therapy. When two diseases co-exist, each requiring diet limitations, the physician must be doubly on his guard not to precipitate the patient into a third illness due to deficiency of vital dietary constituents. This leads naturally to a brief mention of

III. The Patient Himself.—Little need be said in this regard for it is all so obvious. Yet it must be emphasized, and the physician should frequently remind himself that: asthma is an illness which by its chronicity and the varying intensity of its symptoms tends to focus attention on itself, to the neglect of the patient himself, his general health, strength and condition, and the important bearing which his psychic state can have on the course and severity of his asthma.

IV. The Treatment of the Asthmatic Attack.—This might seem to many to be of outstanding importance and therefore deserving of first, rather than last consideration among the general principles of treatment. It is undoubtedly of outstanding importance, but the treatment of the attack can be carried out properly and completely only in the light of all that has gone before. Many times have I seen treatment of the attack fail in the hands of those who knew all about the *symptomatic* treatment but who had overlooked the most obvious axioms of prophylaxis. Thus in a number of cases I have turned the tide in favor of a desperately ill patient *by removing from the oxygen tent* (in one instance oxygen and helium) the *feather pillow* that was slowly but surely choking him to death.

Asthmatic symptoms occur in one of three ways: (1) short, sharp paroxysms, lasting minutes or hours; (2) continuous mild wheezing for weeks, months, or years, usually with slight

to severe paroxysmal exacerbations; and (3) status asthmaticus. Short paroxysms typically arise from intermittent contact with an external cause. Continuous asthma may be due to constant exposure to external causes, or to a combination of external causes and internal causes, notably infection, with or without bacterial allergy. Status asthmaticus designates an intense and prolonged attack of dyspnea, lasting from two to fourteen or more days, usually with fever; with a somewhat scant but very viscid bronchial secretion that defies the patient's efforts to raise it and results in cyanosis or even fatal asphyxia, and with a less mobile type of mucosal edema, which in part at least accounts for the ineffectiveness of treatment with epinephrine. At times there are patches of pulmonary consolidation or of atelectasis. The underlying causes of status asthmaticus are as yet unknown. The writer, on the basis of clinical evidence, believes that its major cause is the severest form of bacterial allergy. He has seen it produced on a number of occasions by even tiny doses of an autogenous vaccine, and has seen this happen twice in the same patient on several occasions.

The *symptomatic treatment* of asthma is directed against certain functional abnormalities, which in turn vary in degree, and to some extent in kind, in the different types of symptom pictures just described. Present in all cases are: (1) *mucosal edema*, probably due to the local action of allergens on blood vessels, and (2) *spasm of bronchial muscle*, probably due at times to local action of allergens on the muscle itself, at others mediated by vagus stimulation. In connection with edema there has been postulated a state of: (3) *increased capillary permeability*. In addition there may be: (4) *altered* (usually increased) *bronchial secretion*, and (5) *anoxemia*. Infection brings with it (6) *inflammatory changes* in the bronchial mucosa. The worse the asthma, the more likely is the patient to show (7) *nervous and emotional unrest*. Prolonged symptoms with consequent starvation and the repeated use of epinephrine may result in (8) *hypoglycemia*, with possibly also (9) *dehydration*.

To combat edema and bronchospasm, by stimulation of the sympathetic nerves, we have available epinephrine, ephedrine, propadrine, benzedrine, neosynephrin and similarly acting

substances; and pituitrin. Atropine can relieve spasm by paralyzing the vagus endings; at the same time it greatly reduces secretions. Theophylline preparations and papaverine act directly on smooth muscle to lessen spasm. Calcium can lessen capillary permeability. Bronchial secretion, especially in chronic cases with infection, is often so viscid as to require excessive cough to raise it, with resultant exhaustion and increased dyspnea of effort. Iodides, and occasionally apomorphine, are used to thin out the sputum. Oxygen with or without helium takes care of the cyanosis. Barbiturates, opiates and general anesthetics have been used to obtain adequate sedation. Surgical anesthesia (rectal administration of ether in oil, or avertin) may effect relaxation of bronchospasm when other measures have failed.

What has experience taught us about the relative merits and proper use of these drugs?

The Acute Asthmatic Paroxysm.—This is best treated with epinephrine. Its quickest results are seen after hypodermic injection. The first principle in its use is: *give it early and as often as needed*. Two to five minims at the first sign of the attack will do more good than a larger dose later. The small dose is less likely to cause disagreeable palpitation and tremor, and so can be used more freely (every five or ten minutes). To insure early administration, *the patient must be taught to give it to himself*: a hypodermic outfit sterilized by boiling should always be available. *For injection purposes use a 1:1000 solution, or weaker*.

Epinephrine by inhalation has proved exceedingly useful because of the ease of administration and its prompt effect. Its successful use hinges on these points: (1) a strong solution (1:100), and (2) an efficient vaporizer that produces an exceedingly small, droplet, smoke-like vapor which is inhaled through the mouth, not blown into the bronchial tree. Two, three or four deep breaths of it will generally be enough; the patient must learn the smallest number that will give relief. The epinephrine which reaches the bronchial tree can give relief without necessarily producing disagreeable vasomotor effects. The excess of epinephrine in the mouth, however, can be absorbed and cause palpitation, etc. The patient should therefore always *rinse out his mouth with water immediately*

after using the vaporizer. Inhalation of epinephrine must be used cautiously in the presence of an acute respiratory infection, because of the far greater absorption of the drug from the inflamed mucosa.

Patients must be warned of the grave danger of mixing bottles and giving 1:100 epinephrine subcutaneously. Death has followed a single dose of 0.6 cc.

Inhalation of *benzedrine* vapor has been found to relieve an asthmatic attack. A special type of inhaler is required. The drug should be used with caution because of the ease of overdosage and possible toxic effects.

Ephedrine and similarly acting drugs given by mouth have little effect except on the mildest attacks of asthma. They are useful, however, in preventing the onset of attacks in patients with frequent paroxysms. For this purpose they should be given regularly, in small doses (e.g. ephedrine hydrochloride, gr. $\frac{3}{8}$) and in combination with a small amount of sedative (e.g., amytal, gr. $\frac{3}{4}$) to avoid nervousness, after meals and not at night (to avoid insomnia).

Pituitrin, alone or together with epinephrine (miii to v of each), will at times produce a quicker and more lasting action than epinephrine alone. This is, however, rarely called for in simple paroxysms. *It should not be used in hypertensives.*

Morphine will relieve an attack of asthma. Practically the only advantage of this lies in the fact that morphine is the only available drug which the doctor happens to have with him when called in the emergency. It has the disadvantages of possible drug addiction as far as the patient is concerned, while the doctor gets a wrong idea of the efficacy of morphine and the indications for its use, so that he gives it freely to patients in status asthmaticus, at times with fatal results.

Atropine is altogether too drying and should therefore not be used as an antispasmodic except in the presence of a watery bronchorrhea. When the sputum is viscid, atropine is not only useless but dangerous.

Only the mildest sedation, and then only when indicated and not as a routine, is called for in paroxysmal asthma. Remember that asthmatics furnish the greatest number of drug idiosyncrasies, and that idiosyncrasies to sedatives rank high among these.

Calcium has proved useless in the treatment of asthma. Other measures than the above are not called for in ordinary acute attacks, and will not be discussed at this point.

As a result of the observation that marked clinical improvement occasionally followed the *instillation of lipiodol* through the bronchoscope into the bronchial tree of asthmatics for bronchography, repeated instillations have been employed in chronic asthma as a therapeutic measure, but without the help of the bronchoscope. The oil is simply dropped through the glottis with a suitable syringe. One enthusiast even teaches the patient how to do it to himself. The procedure has been abandoned by most experienced workers because of the danger of unfavorable effects, including fibrosis, iodism, pneumonia, asphyxia, and even sudden fatal collapse within a few minutes.

What of the inhalation of the smoke of burning *salt peter stramonium powders*? It is mentioned only to be condemned. Although it gives temporary relief, the smoke is irritating to the bronchial mucosa and tends to produce and perpetuate a chronic bronchitis. Sensitivity to the powder has even developed after prolonged use.

In some patients a single dose of *aspirin* (gr. v) will relieve an attack. Those who are relieved pass this information on to other asthmatics. But sensitivity to aspirin is the commonest drug allergy. Sooner or later, then, the information reaches an aspirin-sensitive patient. He takes an aspirin tablet and the asthma promptly becomes worse. Thinking that the severity of the attack calls for a second dose, he takes another tablet and is dead within the hour. Asthmatics should be warned of this danger.

The Symptomatic Treatment of Chronic Asthma.—This offers a more complicated and perplexing problem. Its very chronicity is proof of the fact that all causes have not been found or that they have not been set aside (e.g., infection). Treatment therefore has an endless task and the physician's ingenuity is constantly taxed by the need for finding new therapeutic combinations when older ones lose their effectiveness.

For the milder symptoms, *ephedrine* and similar drugs used in the manner above described are very useful. If the use of

a sedative with the drug fails to prevent the disagreeable nervous symptoms, then smaller doses should be tried, or the drug should be varied. In my experience the synthetic preparations of ephedrine have been less likely to produce bad side-effects. In elderly men these drugs may cause urinary retention, an indication for stopping the drug at once.

Of great value in chronic asthma is the prolonged use of *iodides*. Potassium or sodium iodide should be given by mouth, 2 or 3 grains three times a day. There is no advantage in using any other preparations, especially the expensive organic ones, nor in using any other mode of administration than by mouth.

Some patients have found that they get relief from certain proprietary mixtures containing *antipyrine* and *acetanilid*. They must be warned of the danger of methemoglobin formation (obvious cyanosis) and consequent impairment of respiratory function.

In this group of patients, partly because infection so commonly plays a rôle in their trouble and partly because allergic states are in themselves amenable to some degree to shock therapy, the use of *nonspecific protein shock therapy* is at times found very useful. Candidates for this measure must of course be carefully selected, with particular attention to possible contraindications, such as cardiovascular diseases (notably myocardial weakness, hypertension and arteriosclerosis), advanced age, tuberculosis, etc. The treatment is best carried out by means of intravenous typhoid vaccine, beginning with an initial dose of not more than 10 or 15 million organisms. The desired effect is a chill and fever of 101 to 103° F., lasting two or three hours. If the patient shows any improvement as to his asthma and suffers no unfavorable results otherwise, the treatment can be repeated one or more times, at intervals of five to seven days, and each time with double the preceding dose of vaccine. Such treatments can be given at home but are best undertaken in a hospital. A point to emphasize is that the effectiveness of the treatment appears to depend on sharp stimulation of immune processes and not on a thermal factor; treatment of asthma with mechanical devices for raising body temperature is ineffectual.

A great many therapeutic measures that have at times been

helpful in continuous asthma, and which on the surface appear to be widely diverse in nature, in reality owe their efficacy to the one thing which they have in common: the *nonspecific* protein shock factor. They include such things as non-isotonic solutions (iodides, hydrochloric acid, calcium solutions, distilled or triple distilled water) injected intravenously, or organ or tissue extracts injected subcutaneously or into muscle, tuberculin by subcutaneous injection, autohemotherapy. (Unfortunately their proponents have often been misled into the mistaken idea of a specific relationship between medicament and asthmatic etiology; for example, that the efficacy of an organ extract proves that the asthma must be due to a deficiency of that organ's function in the patient.) *x*-Ray treatment over lungs and spleen probably also acts in the same way. These various nonspecific measures are additional, but exceedingly undependable strings to our therapeutic bow.

In all asthmatics with continuous symptoms an important therapeutic measure is *change of location*, in the hope that the patient will thereby be removed from causes in his environment. The change is best made into a hospital, both because the environment there can be regulated by the physician to contain a minimum of potential allergens and because diagnostic and therapeutic procedures can there be carried out with greater ease and facility.

Whenever, in spite of other measures, the wheezing becomes annoying, recourse is had to *epinephrine*. The same advice applies here as in the case of paroxysmal asthma. Inhalation of vaporized epinephrine has proved an especially welcome aid to these patients, often enabling them to carry on their daily work.

Unfortunately the effect of epinephrine dissolved in water, whether administered orally or by injection, is very transient in these patients, lasting as short a time as an hour or so, particularly at night. With these patients one should try the hypodermic injection of *epinephrine in oil* (0.5 cc. to 2 cc. of a 1:500 suspension of epinephrine in peanut oil—but do not give to those who are peanut sensitive), or of *epinephrine in gelatin* (0.5 cc. to 1 cc. of a 1:500 solution of epinephrine in a gelatin preparation which liquefies and is to be injected subcutaneously at a temperature slightly above that of the body).

These preparations have the property of giving up the epinephrine slowly, so that its action is prolonged. A single dose may therefore give relief for from four to twenty-four hours, with an average of six or eight hours.

There are times, however, when any preparation of epinephrine seems to be ineffective. Patients with chronic asthma at times go into attacks of greater severity. While status asthmaticus has been defined as a clear-cut entity, and in its full-blown state is easily recognizable, there are imperceptible gradations between ordinary asthmatic paroxysms and fully developed status asthmaticus. A patient may pass rapidly—a matter of a few hours—into the severer state; or it may take several days. It calls for clinical alertness to recognize this tendency and prompt action to try to stop it. There are two signs which should serve as urgent danger signals: a change in the sputum, which becomes scantly and more viscid, and a failure of the usual doses of epinephrine.

It is at this time that *morphine* finds its one proper indication in asthma. But it must be given *early*: if given too late in the drift toward status asthmaticus, it does more harm than good. It must be given *alone*, and never together with atropine. The initial dose must be small: not more than gr. $\frac{1}{12}$, and I prefer gr. $\frac{1}{20}$. If the first dose obviously makes the patient more comfortable, so that he breathes more easily and perhaps sleeps a bit, and if epinephrine (which is being given at hourly or even shorter intervals) seems to take hold a bit better, a second equally small dose may be given. *Cocaine* and *dilaudid*, likewise in *reduced* dosage, may be used in the same way and a bit more safely. *No opiates should be given to patients whose history suggests any idiosyncrasy to these drugs.*

I have written this last paragraph not only with care, but with great reluctance, because the opiates administered by non-allergists have been the greatest single cause of death in asthma.

Aminophyllin at times relieves bronchospasm when epinephrine fails. In milder attacks it is effective in oral doses of gr. ii. In severer asthma it is given intravenously: the contents of an ampoule (gr. viiss in 2 cc. of solution) are diluted up to 10 cc. with saline and injected *slowly* into the vein.

Papaverine, one of the opium alkaloids, has a direct relaxing action on smooth muscle, but does not to any great extent depress respiration or cough. It therefore at times proves helpful even when epinephrine fails.

Apomorphine in very small doses—gr. $\frac{1}{60}$ to $\frac{1}{30}$ —does not produce vomiting but increases and thins bronchial secretion. It may therefore be very helpful in relieving severe attacks.

Chronic asthma may successfully resist treatment for years on end. It is therefore not surprising that in desperation a number of *surgical measures* have been tried. These have taken the form of interruption of nerve paths to and from the bronchial tree. Thus far no single procedure has been sufficiently successful to warrant its general adoption. The only approach to a fair success has been bilateral resection of the posterior pulmonary plexus, a very formidable procedure calling for unusual technical skill, and involving considerable risk. Of eleven patients so treated, Rienhoff and Gay¹ report four well, four improved, one unimproved and two dead.

Status Asthmaticus.—This is the major emergency in asthma. A potential threat to life, it calls urgently for every therapeutic resource at our command.

Status asthmaticus most often develops when the patient is in his own home. This is due in part to the fact that there the patient is most likely to suffer prolonged and intense exposure to most of the things to which he is sensitive. In addition, there is usually operative some additional factor, such as an intercurrent respiratory infection, or some insistent cause for worry and despondency, or even a prolonged spell of humid, disagreeable, depressing weather.

The first indication is *immediate hospitalization*, not only to remove the patient from an unfavorable environment, but to make quickly available a number of procedures not easily carried out in the home. The patient should be in a room alone, not in a ward. The room ought to be supplied with filtered air. Bedding and all contents of the room must be in keeping with the patient's allergic pattern. *This must be arranged in advance.*

The matter which most urgently demands treatment is asphyxia. The most effective agent is oxygen. Its adminis-

tration may be by tent, by face-mask, or by intranasal catheter. The simpler methods have the advantage of leaving the patient more accessible for other procedures and for observation. Some patients are terrified by the tent, occasional ones are annoyed by the odor of the tent material. On the other hand, the tent affords better control over the oxygen percentage breathed, affords a pollen-free atmosphere when air filters are not available, and is better adapted for the use of *helium* with the oxygen. The continuance or discontinuance of oxygen administration depends primarily on the patient's color, not his wheezing. As soon as the color becomes good, the oxygen may be discontinued. Intermittent high percentage (50 or 60 per cent) oxygen administration seems to give slightly better results than continuous lower percentages. The use of *helium* as the oxygen diluent instead of the much heavier nitrogen of the air definitely facilitates the breathing of most of these patients.

An important factor in producing the asphyxia in most patients is the viscid secretion which may even give rise to atelectasis. *Bronchoscopy* therefore deserves more attention than it has received in the treatment of status asthmaticus. It has not been harmful, since oxygen can be continuously administered through the bronchoscope, and on several occasions in my experience it has been a life-saving measure.

Surgical anesthesia has proved a valuable aid in relieving status asthmaticus. Bronchospasm is certainly one of the factors in the mechanism of the condition: its relaxation can usually be achieved by profound anesthesia, when epinephrine has failed to do so.

Several anesthetics have been used, notably avertin, ether and cyclopropane. With the latter I have had no experience. Ether has a disadvantage in that, although administered by bowel, its elimination by way of the lungs can have undesirable local effects. On the other hand it is comparatively safe as an anesthetic, it can therefore be used to produce a profound anesthesia with a high degree of relaxation, and the anesthesia lasts long enough to give the patient a good rest. Equal parts of ether and olive oil are thoroughly mixed with an egg-beater. The dose for adults is 5 to 7 ounces of the mixture, whereas 3 ounces suffice for a child of twelve. The

material is instilled into the bowel a dram or two at a time, twenty minutes being required to give the whole dose. Avertin has the same advantages as ether, save for a narrower margin of safety, is more easily administered, and has no irritating effects. The dose is usually that employed for surgical anesthesia: 80 mg. per kilo of body weight.

In approaching the question of anesthesia one must remember that one does not size up the asthmatic candidate for anesthesia along quite the same lines as the ordinary prospective surgical patient. The professional anesthetist stands aghast when he is first asked to give a general anesthetic to a gasping, cyanotic, desperately ill patient with a rapid thready pulse, a low blood pressure, a leaky skin and verging on unconsciousness, and his first impulse is to decline anesthesia and to advise a sedative. Yet a few minutes after the induction of anesthesia, and with the added help of oxygen, the patient is peacefully asleep and all findings are correspondingly improved. He awakens from in four to eight hours, refreshed and fairly comfortable. I have repeated the avertin anesthesia on three successive nights with progressive improvement each time.

When the lungs are "wet," as suggested by many coarse moist râles in addition to the musical asthmatic râles, the *intravenous injection of hypertonic solutions* is useful. *Glucose*, 50 to 100 cc. of a 25 per cent solution, or 25 to 50 cc. of a 50 per cent solution, is to be preferred. Its effectiveness is attributed to the extraction of excess tissue fluid (edema) out of the lungs into the blood stream. *Sucrose* has been similarly employed, but recent observations of renal damage after injection in patients with other conditions should discourage its use in asthmatics.

Venesection, especially in case of "wet" lungs, is a procedure that has not received the attention it deserves. Its results are at times dramatic. One should remember the principle set forth by the old phlebotomists: that 10 ounces withdrawn *rapidly* was more helpful than 20 ounces removed slowly.

When the patient comes to the hospital after several days of severe asthma during which he has taken little food or nourishment, both *hypoglycemia* and *dehydration* may be pres-

ent. A blood sugar estimation is therefore in order. If the blood sugar is under 80, glucose should be given: in hypertonic solution if there are "wet" lungs, in 5 per cent solution if there is dehydration. In the latter case a total of 1000 cc. is given *slowly* by venoclysis (40 drops per minute). It is usually unnecessary to give salt by vein, and at times unwise (more tissue edema).

It is characteristic of these patients that they are helped little or not at all by epinephrine; they are said to be "epinephrine-fast." This is, however, not absolutely true in many cases. The *intravenous* injection of epinephrine is usually followed by some relief. Such administration must, however, be in small doses, often repeated. I have found it helpful to put the epinephrine into the 5 per cent glucose solution which is being given by drip. Thus 2 cc. of 1:1000 epinephrine are given in the first 60 cc. of glucose solution, which should take thirty minutes to flow into the vein (*i.e.*, 1 minim of epinephrine per minute). Thereafter, the rate of administration of epinephrine should be 1 minim or less every two minutes, attained by adding 1 cc. or less to every 60 cc. of glucose solution given in each thirty minutes. Or the injection of epinephrine may be made directly into the vein, leaving the needle in position, and never giving more than 1 minim at a time or in a single minute.

Aminophyllin, given intravenously as above described, is at times very effective in status asthmaticus. It never does harm and it may give great relief for a number of hours.

Morphine, Dilaudid, Codeine, and other Opiates should never be given in Status Asthmaticus. A single dose, by slowing the respiration and lessening the cough reflex of a strangling patient, may kill him within an hour. There should be a standing order in hospitals forbidding the ordering of opiates by interns for asthmatics without previously consulting an older staff member.

The favorable termination of status asthmaticus is usually heralded by the return of effectiveness of epinephrine as ordinarily administered, by the expectoration of large amounts of mucoid sputum that becomes thinner in consistency as it increases in amount, and by the return of the temperature to normal. The more fever there has been during the attack,

the greater is the degree of improvement, even complete relief, after the attack, and the longer the subsequent period of relief.

Application of General Principles to the Individual Patient.—To write at this point of the application of these therapeutic principles to the individual patient is not an easy matter, if one is to avoid unnecessary repetition or trite statements about clinical skill, judgment and individualization. I shall therefore limit the discussion to a few points of advice proved useful by experience.

The first principle is a *complete diagnosis*. The earlier in the course of the disease that this is sought for, the less complicated is the problem and the easier its solution. The physician who sees the patient in his *first* attack has therefore at once the best opportunity and the greatest responsibility. It is wise to tell the patient before giving him the injection of epinephrine that the relief to follow, dramatic though it may be, will only be temporary, and that future attacks will come with increasing frequency and severity and bring serious complications in their wake if the underlying causes are not discovered.

Physician and patient must then outline a *plan of observation and study*. From the patient's point of view this means a careful recording of all circumstances attending an attack while those circumstances are fresh in his mind. The physician should guide the patient in making such records significant: as, for instance, when the patient briefly states that trouble began "at work" or just after "going to bed," the physician should inquire into the details of the patient's exposures at work that day, or the nature of the bedding in question. The latter point must never be determined by the mere statement of the patient, but by inspection of actual samples of the contents of pillows and mattress. Unless relief is early and complete, the physician should make a personal inspection and survey of the patient's working and home environment. When diagnostic tests have been performed, a careful daily recording by the patient of all contacts, foods eaten, activities and symptoms, supplemented by an equally careful scrutiny of these records and of the patient's environment by the physician, is the only way in which the full benefit of skin test results can be achieved. Too much emphasis can-

not be placed on the matter of a systematic, concise recording of all events in the patient's life, including therapeutic procedures.

The patient must be completely advised of all points that bear on his case. A common mistake is to tell him only the foods to which he reacted, without telling him the foods to which he did not react and to which he must limit his diet; or to advise him what bedding materials he must avoid, without specific directions as to what bedding to use.

Patients with paroxysmal asthma need not be hospitalized, although it may at times be desirable to note the effect of change of environment, but can be studied as ambulatory patients in intervals between attacks. Patients with continuous asthma, however, should be hospitalized promptly and preferably for a period of about two weeks. The patient with continuous asthma is obviously beset by severe and continuous causes, has probably already suffered secondary complications, and is having the reflex paths, involved in the asthmatic syndrome, become rapidly accustomed to respond to less and less of a stimulus. There is therefore urgent need to break the vicious circle promptly and completely. This can best be accomplished in a controlled (hospital) environment. At the same time the patient can receive more intensive instruction in how to take care of himself, and the lessons somehow seem to be much more impressive when imparted in the hospital setting.

Hospitalization greatly facilitates diagnostic studies and observations on the results of treatment measures, but one must be sure that treatment does not interfere with the results of studies. Thus skin tests may well give negative reactions if performed within an hour of a dose of epinephrine.

Whenever an asthmatic patient is hospitalized, it is the referring physician's duty to get information about the patient's sensitivities *in writing* to the hospital physician *before* the patient is admitted. The patient may be far too ill to protect himself against his known enemies.

Every time the patient changes his location and every time some new measure of treatment is instituted there is danger of a serious therapeutic error: that some previously instituted item of treatment is forgotten or allowed to lapse. This is

most likely to be a matter of diet or environmental allergen. It is the task of the physician to keep in hand all therapeutic leads at all times.

When for no obvious reason a patient gets worse, one must keep in mind the possibility of a newly arisen *psychologic factor*. Thus in a young woman with mild asthma due to pollen and house dust, severe asthma, going on to status asthmaticus, followed the breaking of the engagement by her fiancé. In another instance, when change of location had produced complete relief apparently by avoiding local allergens, symptoms recurred when a cantankerous relative followed the patient to the same city, although not to the same house.

Whenever some *intercurrent factor* severely affects the patient, whether that be an acute cold, other illness, or trauma, or whether it be a cause for worry and mental depression, there needs to be a sharp revision downward of the dosage by injection of vaccines, dust and pollen extracts, etc., because of the greatly increased possibility of an unfavorable reaction under the circumstances. The reduction may have to be as low as a tenth of the last preceding dose. But the treatment should not be omitted, except perhaps for a delay of at most three or four days in the presence of an acute infection. To stop treatment for more than twelve or fourteen days means the loss of valuable ground. When the emergency has passed the dosage may be rather promptly stepped up to its former levels.

The question is often put: what is the best *climate* for the treatment of asthma? There is no climatic treatment of asthma. There is only climatic treatment for the individual asthmatic. What may be a favorable place for one patient may prove quite the reverse for another. Years ago Hyde Salter recognized this when he suggested that an asthmatic try a climate with characteristics the opposite of the ones to which he was accustomed. A few guides in selecting a climate may be ventured, but always without any advance guarantee. An equable climate without severe storms is preferable for most patients, since the asthmatic is often troubled by a falling barometer, symptoms increasing proportionally to the speed of the fall. This may be at least carried by the high winds present at such times. is prob-

ably also a direct effect on the asthmatic himself. Smith² has shown that there is a positive water balance in the body with reduction of barometric pressure. I wish to point out that this would increase the amount of edema which a given quantity of allergen could produce in the mucosa of an asthmatic. At high elevations, air-borne allergens, such as pollens, mold spores and dust, are less numerous and the humidity is relatively low, so that numerous mountain resorts for asthmatics have arisen. On the other hand, asthmatics with emphysema and greatly reduced vital capacity should never go to an altitude over 3000 feet; in fact they are best off at or near sea level. Patients with considerable amounts of sputum, and especially if there is attendant bronchial infection, do well in a dry climate with sandy soil and at an altitude under 3000 feet (e.g., parts of southern Arizona or southern California). On the other hand, if the patient's sputum be scant and inclined to be viscid, a moister climate and closer to sea level is better (Georgia, Florida, Gulf Coast). High humidity, and especially fog, are badly borne by most asthmatics. Whenever a climatic change is planned, every effort must be made that the patient does not blunder into the same environmental allergens in his new locality that caused his symptoms at home, or into new ones peculiar to the new surroundings but possibly related to the old allergens. If the patient is completely relieved by the climatic change, he should remain in his new location for at least four to six months before essaying a visit to his home and should be prepared to flee at the first sign of recurrence of symptoms.

Finally, a word about a most important topic: *prophylaxis*. Asthma rarely appears full-blown in a person who up to that moment has been completely well. Nearly every asthmatic gives a history of months or years of upper respiratory allergy, such as hay fever or allergic rhinitis. The latter may be evidenced merely by bouts of half-a-dozen sneezes at certain times of the day; or there may be more obvious nasal difficulties, such as nasal polyps or chronic sinus trouble. The proper and continued treatment of these upper respiratory sensitivities along recognized allergic lines will be the ounce of prevention that is far superior to the pound of asthmatic cure.

In conclusion, let it be emphasized that both physician and

patient must realize early and to the fullest extent that the successful treatment of asthma calls for thoroughness of study; cooperation of specialists and physician and of physician and patient; constant consideration of a multiplicity of factors; perseverance in therapy; nicety of judgment; and critical evaluation of the individual's problem: all of these to a degree not exceeded in the realm of clinical medicine.

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PRURITUS: DIFFERENTIAL DIAGNOSIS AND TREATMENT

"PRURITUS" is a term synonymous with itching, and is a symptom and not a disease. Carlyle once stated that the height of human happiness is "to scratch the part that itches." While itching may be pleasurable to a certain point, it may also cause immeasurable agony, result in partial or almost complete inability to sleep, and completely upset the nervous stability and general health of the affected individual. As Shakespeare said, "the itch hath murdered sleep."

Lord Horter, in the Prosser White oration of 1935,¹ pointed out that itching may be regarded as an almost normal function of the skin in health. Who is there that has not been annoyed at the most inconvenient times with an almost uncontrollable desire to scratch some small part of his anatomy such as the nose or an ear? More than a half century ago Neumann² called attention to the mild pruritus that is frequently felt after a full, rich meal in one of sedentary habits and the transitory itching that is often felt after violent exercise. Lord Horter pointed out that itching may be caused by "too little sweating and too much sweating, too dirty a skin and too clean a skin."

DIFFERENTIAL DIAGNOSIS

Pruritus was defined by Bronson in 1891 as "a nervous derangement involving some molecular or anatomical change that disturbs normal relation." Confronted with a patient whose chief complaint is pruritus, the physician must make a planned search for the cause of this "molecular or anatomical change." The following outline of possible causative factors may prove helpful:

CAUSES OF PRURITUS

1. Dermatoses accompanied by severe itching:
 - (a) Urticaria, scabies, eczema, etc.
2. Changes in the skin unaccompanied by any true dermatosis:
 - (a) Senile pruritus.
 - (b) Pruritus hiemalis (winter itch) and pruritus aestivalis (summer itch).
 - (c) Bath pruritus.
3. Endogenous toxins, caused by:
 - (a) Drugs (opium, cocaine, alcohol).
 - (b) Focal infections.
 - (c) Lymphatic disease (Hodgkin's disease, leukemia, etc.).
 - (d) Diabetes.
 - (e) Disease of the liver or gallbladder.
 - (f) Nephritis or renal calculus.
 - (g) Intestinal toxemia.
 - (h) Hyperuricemia. (?)
4. Functional or organic nerve disease.

Dermatoses.—The dermatologist confronted by a patient with the chief complaint of pruritus has the patient strip completely to ascertain if a dermatosis or parasite is responsible for the itching. This may not be readily perceived unless close attention is given to minute details. The patient with a recently acquired scabies may show only a few scratched papules or a few isolated burrows. Microscopic study of the contents of a burrow may be necessary to prove the diagnosis of scabies, and the finding of the *Acarus*, or any portion of an *Acarus*, its ova, or excreta, suffices to make a positive diagnosis. The presence of scratch marks on the body calls for an examination of the underclothing for the presence of pediculi. Great was the embarrassment of a well known internist, who asked for a dermatologic consultation for a hospitalized patient complaining of night pruritus, when the bed was found to contain *Cimex lectularius* (bedbugs). The presence of a few wheals with central puncta on the trunk of the patient offered the necessary clue. Pruritus associated with true dermatoses will be passed over with this brief discussion.

Changes in the Skin Unaccompanied by a True Dermatitis.—The term *senile pruritus* is used rather promiscuously for any persistent itching occurring in an elderly person; it is supposed to be due to drying and atrophic changes in the skin. However, it is always a mistake to come to this conclusion too hastily, for this is the very type of patient who would be likely to have one of the diseases included in group 3 of the foregoing table. Luithlen³ has pointed out the possibility that the itching in a true case of *pruritus senilis* may be due to a deficiency of silicic acid in the tissues.

In *pruritus hiemalis* and *pruritus aestivalis* there is a definite relationship between the exciting cause and the effect. *Pruritus hiemalis* presents itself at the beginning of cool weather and persists into the late spring. Stellwagon observed that this condition occurs chiefly in individuals whose skin sweats too little and is lacking in natural oiliness. *Pruritus aestivalis*, which is much less common, occurs in extremely hot weather and may possibly be due to irritation from sweat.

Pruritus following a bath was first described by Stellwagon,⁴ who stated that the actual cause is the water and that this condition occurs in patients with a dry, harsh skin. Even softening or alkalizing the water by adding starch, soda, or bran seems to have no effect in preventing the attack. I am convinced that the daily bath habit is causative in many of the cases. Persons with a naturally dry skin only increase the degree of dryness by a daily bath, which is usually not required.

Endogenous Toxins.—Perhaps the chief interest in this subject centers around group 3 of the foregoing table. It must be remembered that the patient who suffers for a prolonged period from pruritus will show a secondary eczematization of the skin, with excoriations, lichenification and pigmentation. If the pruritus is of recent origin these cutaneous manifestations will be lacking. In this group the pruritus is probably caused by circulating toxins in the blood and a most exhaustive search may be necessary to unearth the particular etiologic factor.

Textbooks tell us that certain *drugs*, such as opium and its alkaloids and cocaine, may give rise to pruritus. It is paradoxical that morphine will often act almost specifically in tem-

CAUSES OF PRURITUS

1. Dermatoses accompanied by severe itching:
 - (a) Urticaria, scabies, eczema, etc.
2. Changes in the skin unaccompanied by any true dermatosis:
 - (a) Senile pruritus.
 - (b) Pruritus hiemalis (winter itch) and pruritus aestivalis (summer itch).
 - (c) Bath pruritus.
3. Endogenous toxins, caused by:
 - (a) Drugs (opium, cocaine, alcohol).
 - (b) Focal infections.
 - (c) Lymphatic disease (Hodgkin's disease, leukemia, etc.).
 - (d) Diabetes.
 - (e) Disease of the liver or gallbladder.
 - (f) Nephritis or renal calculus.
 - (g) Intestinal toxemia.
 - (h) Hyperuricemia. (?)
4. Functional or organic nerve disease.

Dermatoses.—The dermatologist confronted by a patient with the chief complaint of pruritus has the patient strip completely to ascertain if a dermatosis or parasite is responsible for the itching. This may not be readily perceived unless close attention is given to minute details. The patient with a recently acquired scabies may show only a few scratched papules or a few isolated burrows. Microscopic study of the contents of a burrow may be necessary to prove the diagnosis of scabies, and the finding of the *Acarus*, or any portion of an *Acarus*, its ova, or excreta, suffices to make a positive diagnosis. The presence of scratch marks on the body calls for an examination of the underclothing for the presence of pediculi. Great was the embarrassment of a well known internist, who asked for a dermatologic consultation for a hospitalized patient complaining of night pruritus, when the bed was found to contain *Cimex lectularius* (bedbugs). The presence of a few wheals with central puncta on the trunk of the patient offered the necessary clue. Pruritus associated with true dermatoses will be passed over with this brief discussion.

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Textbooks tell us that certain *drugs*, such as opium and its alkaloids and cocaine, may give rise to pruritus. It is paradoxical that morphine will often act almost specifically in tem-

porarily relieving pruritus. Phenobarbital likewise may both relieve and produce pruritus. During the years of prohibition it was not uncommon to observe pruritus following the ingestion of cheap, synthetic alcoholic liquors.

Focal infections are blamed for many of the ills of mankind, but I have observed cases in which the extraction of an abscessed tooth relieved pruritus of otherwise undiscoverable etiology.

In the *lymphogranulomatous diseases*, itching is often the first symptom, and the underlying disease may not become manifest for a variable period of time. The late Dr. Jay F. Schamberg and I were once consulted by a middle-aged woman with a chief complaint of pruritus who was proved to have Hodgkin's disease. She had had itching for many months, and several reputable physicians who had seen her previously stated that there had been no evidence of the underlying Hodgkin's disease in their examinations. Too well do we know that a general pruritus may be the precursor of granuloma fungoides, a disease which is invariably fatal.

Even though its presence may be suspected in a patient with a chief complaint of pruritus, *diabetes* may be easily overlooked and not detected upon routine examination of the urine. A blood sugar determination is always in order, although in a series of sixty cases in which the chief complaint was pruritus, I⁵ found an increase above normal limits in only two cases.

When jaundice is present as an accompaniment of *disease of the liver or gallbladder*, generalized itching will invariably be experienced. However, the pruritus often precedes the development of color changes in the skin, and here again only careful examination will lead to early diagnosis. A case of pruritus has been described by Zeisler⁶ in which examination of the blood disclosed an excess of bilirubin when there was no jaundice. Because of gastric symptoms, laparotomy was performed and a partial obstruction of the ampulla of Vater was found, together with marked pancreatitis. The operation gave almost complete relief from pruritus. In this case, although there was no jaundice, there was sufficient obstruction to the flow of bile to produce the excess of bilirubin in the blood. Schamberg, in *Unna's Fiftieth Anniversary Festschrift*,

reported a case of "Persistent Pruritus With Urobilinuria Without Jaundice."

It is well known that pruritus may be an early symptom of acute *nephritis*. It may also be one of the earliest signs of *renal calculus*. Itching has also been observed in connection with the presence of *Bacillus coli* in the urine and excessive oxaluria. The urine should always be examined for albumin, sugar, bile acids and urobilinogen.

Intestinal toxemia is a broad term, but it is used here to include various disorders of the alimentary tract such as indigestion, flatulence and constipation. It is widely recognized that pruritus may occasionally be due to poisons absorbed from the alimentary tract. MacLeod⁷ has suggested that certain articles of food are apt to produce pruritus and lists the most important as follows: shellfish, tinned fish, oily fish, spices, curries and highly seasoned dishes, mustard, cheese, sausages, strawberries, tomatoes, acid wines, malted liquors, spirits and coffee.

In the series of sixty cases of pruritus studied by the writer and reported upon previously⁵ the uric acid of the blood was above normal limits (3.7 mg. per 100 cc.; Folin and Wu) in twenty-six cases, or 43 per cent. In these twenty-six cases there was no other discoverable cause for the itching, and nineteen of these patients were partially or completely relieved of their itching by a purine-free diet, although I must admit that local antipruritic remedies were also used in the majority of the cases. Further study of the relationship of *hyperuricemia* to pruritus is necessary before any conclusions can be drawn.

There are a few other conditions in which pruritus may occasionally be present, among the more common of which are *tuberculosis*, *carcinoma*, *pregnancy*, *ovarian disease* and *prostatitis*. In such cases, pruritus is rarely a primary manifestation. Miller⁸ has reported a case of generalized pruritus in which *Clonorchis sinensis* (liver flukes) were found in the stool and duodenal contents.

Functional or Organic Nerve Disease.—It is unfortunate that medical science is not sufficiently exact to permit discovery of the causes of the pruritus in all cases. When the etiology remains undiscovered, the tendency is to classify the

cause as neurogenic or psychogenic. Undoubtedly, many cases of pruritus are of purely nervous origin, but such a conclusion should be reached in a given case only when there is marked evidence of nervous indisposition and when all other etiologic possibilities have been ruled out. Darier⁸ has said that "*nervous pruritus* is commonly observed among social workers, failures, unhappy inventors, mental defectives, as a result of too much work or too much play and as a sequel of emotional disturbance; the original depression is aggravated by the constantly recurring distress and by insomnia, leading to neurasthenia and melancholia." Occasionally there is a true organic cause, such as hemiplegia, brain tumor, general paralysis, or tabes.

The fact must be recognized that there are cases of pruritus where the pruritus seems to stand alone as a sole symptom and of unknown etiology. This type is called *primary, essential, or idiopathic pruritus*.

TREATMENT

By keeping in mind the etiologic possibilities and by attempting to classify properly the case in question, the treatment of pruritus is simplified, although it is apt to prove difficult even under the most favorable conditions. No matter what the primary cause may be the nervous stability of the patient is apt to be more or less deranged as a result of the constant torment; the skin is excoriated and sometimes thickened as a result of the scratching. These factors may continue the pruritus long after the true cause is discovered and removed.

Of the internal remedies, *bromides* and *Cannabis indica* are of paramount value. They serve to quiet the nerves. Bromides may be given by mouth in doses of 5 grains three or four times daily, or they may be given intravenously, 5 cc. of a 10 per cent solution in physiologic salt solution being given the first day and 10 cc. being given on the second and following days. Tincture of *Cannabis indica*, which is strongly recommended by Crocker, is often of great value. Beginning with a dose of 10 minims t. i. d., the dose may be increased 2 minims daily until from 25 to 30 minims are being taken three times

daily. In extremely stubborn cases *morphine* will often prove a valuable remedy. *Pilocarpine*, *physostigmine*, and *ergotamine tartrate* are other drugs which may be tried.

General dietetic and hygienic measures are of importance. The *diet* will necessarily depend upon the findings in a given case. Avoidance of red meats, internal organs, and sweets is recommended. Attention should be given to the intestinal tract. The bowels should be kept well open, and if there are symptoms of intestinal stasis, high colonic irrigations may prove of great value. When there are symptoms of starch intolerance, sugars and starches should obviously be deleted from the diet.

In difficult cases the writer has found that *foreign protein therapy* will result in the abatement or entire cessation of the pruritus. A 4 per cent suspension of milk protein may be used, from 1 to 5 cc. being injected into the deep muscles of the buttocks at intervals of from three to seven days. This may or may not produce a slight febrile reaction, but the patient should be warned of the possibility of this happening. Two patients who failed to respond to any other therapeutic measures and all of whose examinations failed to reveal any etiologic factors were entirely cured by injections of milk protein. The rationale of this procedure is as yet little understood, and it must be used empirically.

Autohemotherapy, consisting of the withdrawal of from 10 to 20 cc. of blood from a vein in the arm and its immediate reinjection into the buttock, is occasionally helpful. Sulzberger and Wolf¹⁰ found that generalized pruritus, even though due to lymphogranulomatosis or abdominal malignancy, responded surprisingly well to this treatment.

Basing his treatment on the deficiency of *silicic acid* in the tissues of elderly people, Luithlen injects this acid for senile pruritus. A 1 per cent solution is used, the first injection being 0.5 cc. and the dose being increased to 1 cc. and 2 cc. upon subsequent injections, which are at two-day intervals. A simple but unusual therapeutic procedure for the treatment of senile pruritus is suggested by Veress¹¹ who finds that the itching is invariably relieved by rubbing the skin over the prurigenous area with a soft brush for from twenty to twenty-

five minutes two or three times daily. This *brushing* removes the epithelial debris which Veress believed is the cause of the itching.

Based on the assumption that senile pruritus is due to a disturbance of metabolism, Borak¹² advised *irradiation of the hypophysis and thyroid*. Of ten patients so treated, eight were relieved within a week and remained cured.

Klauder¹³ recommends *psychotherapy* in treating pruritus of nervous origin in the hope of producing a transformation of mental attitude and dispelling the fear and dread of itching. It has been pointed out by Yaskin¹⁴ that "anxiety is the central symptom of nearly all the neuroses and psychoneuroses," and he points out that this is of fundamental importance in the management of cardiac neuroses. The same may be said to be true of cutaneous neuroses, and the aid of a psychiatrist should be sought.

External therapy is vastly important as it will usually subdue and occasionally will remove the pruritus no matter what the cause may be. One of the simplest procedures consists of the use of a soothing bath. Starch, soda, or bran may be added to half a tub of lukewarm water and the patient permitted to remain in this bath for from fifteen to thirty minutes once or twice daily. This is followed by patting the body dry with a soft towel. When bran is used, it should be placed in a thin mesh bag. The most serviceable external remedies are menthol, camphor, phenol, tar and alcohol, but care must be taken not to employ strengths sufficient to inflame the skin. The addition of 0.5 to 1 per cent phenol to olive, linseed, or cottonseed oil, or to equal parts of an oil and lime water, makes a useful antipruritic application. Calamine lotion is rarely helpful, as it tends to dry the skin and gives only very temporary relief, but *calamine liniment* may often be used with benefit, as in the following prescription:

R	Phenolis.....	5j
	Pulv. Calamin.....	
	Pulv. Zinc Oxid..	ss
	Liq. Calcis.....	
	Ol. Olivac.....	ss q.s. ad 3vij
	Emulsify.	

Unna's glyccero-gelatin paint may be applied to fairly widespread pruritic areas with, sometimes, complete relief. After

applying the wetted preparation with a paint brush a thin layer of ointment may be painted on. Renewal will be necessary in from average-four to four-eight hours, although on the arms or legs it may remain for several days.

When pruritus is caused by an unusual dryness of the skin and in senile pruritus, frequent bathing must be avoided and the skin must be kept soft by frequent anointments of an oil or 10 per cent ointment of urea in cold cream.

Ultraviolet light is usually helpful in regional pruritus, but it cannot be used over large pruritic areas.

Remember that there can be no routine therapeutics for a symptom which may be of varying degrees of intensity and which may be due to such a variety of causes. Patient study of each case and reassurance are all important.

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CLINIC OF DR. JOHN B. LUDY

PENNSYLVANIA AND EPISCOPAL HOSPITALS

DISEASES OF THE SCALP

SOME of the cutaneous disturbances have a specific regional predilection which is of clinical significance in diagnosis. The adult scalp is the site of seborrhea, seborrheic dermatitis, psoriasis,



Fig. 103.—Twenty-six-year-old patient with endothelioma capitis of four years' duration.

riasis, eczema, furunculosis, various forms of alopecia, hair dye dermatitis, warts, sebaceous cysts, lupus erythematosus, folliculitis decalvans, endothelioma, carcinoma, and melanoma. The scalp of the child, on the other hand, is frequently affected with ringworm, pediculosis and impetigo (Figs. 103-105).

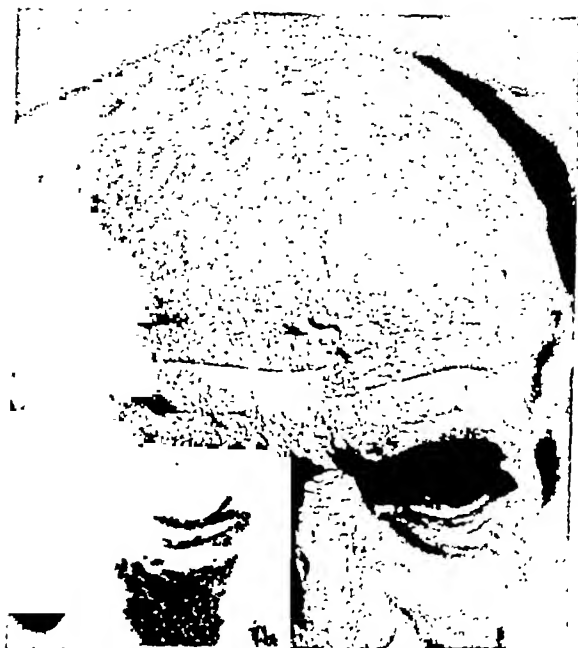


Fig. 104.—Partial baldness resulting from folliclis (a tuberculide).



Fig. 105.—Ringworm of the scalp.

SEBORRHEA

Seborrhea is more of a functional disturbance than a disease. It is a manifestation of an increased output of sebum by the overactive sebaceous glands. The condition is of comparatively little significance, appearing on the child's scalp as a greasy scale (*vernix caseosa*—cradle cap) and leading to *pityriasis capitis* or dandruff in adults.

The skin of seborrheic subjects is often dirty in appearance, assuming a yellowish or brownish hue. The pilosebaceous follicles are enlarged. Plugs of undissolved sebum exude from the region of the *ala nasi* whenever these enlarged sebaceous follicles are squeezed.

H. W. Barber described two types of seborrheic patients: "the one, usually fair complexioned, is flushed, robust, usually active and in later life plethoric; the other, usually dark, is pallid, coarse skinned, pigmented and indolent."

Seborrhea commonly occurs in brunettes and is often associated with hypertrichosis. The condition is unquestionably of endocrine origin and appears to be influenced by gonadal hormones.

Seborrhea is a predisposing causative factor in a group of well-known cutaneous diseases. It is ideal for the growth of microorganisms, thus enabling the ordinary harmless cutaneous saprophytic bacteria to become so pathogenic as to produce dermatitis.

Seborrheic Dermatitis (*Eczema Seborrhoicum*, *Seborrhea Corporis*).—This is a disease of the skin produced by the *Pityrosporum* of *Malassez*. It is characterized by scaling and the hypersecretion of sebum. The areas of predilection are the scalp, eyebrows, nasolabial fold, and the axillary, presternal and pubic regions.

Seborrheic dermatitis of the scalp appears in its mildest form as a fine, powdery scaling or flaking of the horny layer of the integument with no signs of inflammation. The condition is popularly known as "dandruff." It is annoying on account of the itching which is occasionally present. The scales are seen on the clothing. They form well-circumscribed patches which may spread over the entire scalp. Inflammatory changes make the scalp red and edematous. In this case, the scales become caked to form irregular patches whose base

is purplish. The patches extend beyond the scalp margin. The scalp may ooze sufficiently in severe cases to wet the bed linen. The hair of the affected areas becomes lustreless and brittle, tending to shed, especially in males. The defluvium begins on the vertex of the head and temples, gradually spreading over the entire scalp until a mere fringe of hair is left on the sides and back of the head. Seborrheic dermatitis of the scalp is the chief cause of premature baldness in males. It is known as "seborrheic alopecia" or "calvities."

The disease is contagious. It can spread from the scalp to the skin surface and may also be conveyed from one individual to another by contaminated combs and brushes. The infection is progressive, resistant to treatment, and frequently recurs.

Seborrheic dermatitis must be differentiated from psoriasis and ringworm. Psoriasis occurs as well defined, reddish, scaly patches covered with coarse, white scales. The patches in seborrheic dermatitis are pale and ill defined, fading into the adjoining healthy cutaneous surface. The scales are delicate and greasy. Psoriasis is rarely confined to the scalp because other parts of the body, such as the extensor surface of the limbs and sacral region, are always involved. Seborrheic dermatitis must be differentiated also from tinea tonsurans. The patches of ringworm are bald or scaly and partly covered with remains of diseased hair. The differential diagnosis is further confirmed by microscopic examination of the involved area or by a Wood's glass lamp under which the fungus-laden hair becomes fluorescent.

Treatment.—There is no specific internal treatment for seborrheic dermatitis. Gastro-intestinal disturbances which may be present are corrected. The diet should be bland, nutritious and rich in fresh vegetables and fruits, and should exclude milk or foods containing milk, cane sugar, cocoa, chocolate, pork, ham, bacon, sausage, game, spices and rich sauces. Alcoholic and aerated waters of any form are prohibited.

The local treatment of a seborrheic infection of the scalp varies in conformity with the severity of the infection and the age and sex of the patient. The principle of local treatment is the same in all cases, namely, destruction of microorganisms

and regeneration of the epidermis. Treatment is continued in modified form for some time after apparent recovery.

An excellent treatment of the scalp is to prescribe a *lotion* for daily use and a weekly application of an oil or a pomade the night before a shampoo. As a rule, the scalp should be washed once a week. Whenever the hair is excessively oily, the shampoo may be given twice a week or daily for a period of several weeks. The following spiritus soap lotion is employed when the scales are dry:

R Soft soap	2 ounces	60 Gm.
Spt. vini rect. 50%	1 fluid ounce	30 cc.
Thymol	60 grains	4 Gm.
Oil of lavender	60 minims	4 cc.

M.S. This lotion is rubbed into the scalp by the fingers or by a small piece of sponge until a lather is formed and then rinsed with warm water.

A tablespoon of the following mixture is added to a quart of water and used as a shampoo whenever the scalp is inflamed:

R Tincture of quillaia	15 min.	1 cc.
Borax	15 gr.	1 Gm.
Spt. vini rect. 50%	1 oz.	30 cc.

The following ethereal preparation is more effective in cases where the scalp is greasy:

R Ether	120 minims	8 cc.
Aqua ammonia fort	20 minims	1.2 cc.
Soft soap	2 ounces	60 Gm.

The hair should be cut and washed with a saturated solution of boric acid when the scalp is greatly inflamed and oozing is present. One grain of bichloride of mercury added to every 8 ounces of the saturated solution of boric acid greatly enhances its bactericidal property.

Robert M. B. MacKenna prefers the following lotion in acute attacks:

R Collosol sulfur (Crookes)	1 ounce	30 Gm.
Aqua distillata	q.s. 8 ounces	240 cc.

M.S. To be applied freely. Cover areas with lint soaked in this solution.

The following stimulating antiseptic toilet lotion is rubbed into the scalp in mild cases before the hair is brushed after the shampoo:

R Salicylic acid	30 grains	2 Gm.
Castor oil	30 minims	2 cc.
Bay rum	q.s. 6 fluid ounces	180 cc.

Considerable caution must be exercised in the choice of pharmaceutical preparations. Resorcin or betanaphthol should not be used on blond or white hair. Mercury and sulfur should only be combined in the same preparation if the red or yellow oxide of mercury is employed.

A moderate amount of alcohol in scalp lotions is antiseptic and helpful. Any drying action resulting from the use of alcohol may be avoided by the addition of oil to the lotion.

Oils in scalp lotions for women are avoided because they make the hair stringy. Oils are best applied in women immediately before shampooing. Brilliantine may be used in place of oil.

The following lotion is useful in cases in which oiliness of the scalp is excessive.

I½ Mentholis	3 grains	0.15 Gm.
Liq. carbonic detergens	2 drams	8.00 Gm.
Hydrarg. chlor. corros.	2 grains	0.12 Gm.
Spts. vini rect.	q.s. 8 fluid ounces	240 cc.

The addition of 5 per cent of acetone or 10 per cent of carbon tetrachloride to this lotion greatly increases its effect.

The benefits from ultraviolet therapy are widely recognized. The scalp should be washed the day before treatment. Mild erythema doses are given at intervals of five days to the vertex and sides of the scalp. Whenever crusting of the scalp is present, recovery is hastened by the use of unfiltered roentgen rays. This treatment should only be administered by an experienced roentgenologist.

PEDICULOSIS CAPITIS

Pediculosis capitis is produced by the pediculus or louse. It is characterized by local itching and the presence of insects and nits in the hair. The nits (eggs) are millet-seed in size, shiny, egg-shaped bodies with their small end firmly cemented to the shaft of the hair.

Pediculosis capitis is often complicated by cervical adenitis, eczema, impetigo and furunculosis.

Treatment.—The application of 2 per cent ammoniated mercury ointment for a period of several days destroys the living insect. The nits or ova are resistant to soap and water, but can be destroyed by diluted acetic acid or vinegar in proportions of 1 part acetic acid or vinegar to 4 parts of water.

R. Sabouraud states that the free application of plain vaseline destroys the parasites because it suffocates them. He adds 50 drops of xylol to 50 Gm. of white vaseline. This destroys the nits as well as the insects.

The following method has proven most satisfactory in female children or in adults with long hair: The child is laid on his back on a table, with the head projecting over the edge and the hair hanging down over a bucket. Pour a quart or more of an aqueous solution of carbolic acid (1:40) over the head so as to drain through the hair. The hair is then thoroughly dried and the devitalized nits are removed with a dust comb moistened with vinegar. A 1:4000 solution of bichloride of mercury may be substituted for the carbolic acid solution.

Mild cases are treated with tincture of delphinium in which the hair is soaked twice daily for a few days.

Equal parts of kerosene and mineral oil applied at bedtime for a few days is very efficacious.

Impetigo and furunculosis, which so often accompany pediculosis capitis, usually disappear when the pediculi have been destroyed. The treatment is therefore the same as in pediculosis capitis.

TINEA CAPITIS

Ringworm of the scalp is an infection produced by different species of vegetable parasite. The microsporon is the more common parasite. It is a disease of childhood and is rarely found after the age of puberty.

The following diagnostic clinical findings are usually present in tinea capitis: (1) scaliness, (2) broken off hair covered with a grayish sheath, (3) prominent hair follicles, and (4) partial baldness. Itching is rarely present. The lesions may be single or multiple, and they vary in size from a dime to a silver dollar (Fig. 105).

Sources of infection are usually a pet animal, such as a cat or dog, contaminated head wear, combs, brushes and bed linen.

Treatment.—Treatment consists in (1) daily shampooing of the scalp with soaps containing tar, phenol or bichloride of mercury; (2) epilation of involved hairs, including some of the hair surrounding affected areas; (3) application of parasiticide ointments and lotions. Vaseline ointments containing betanaphthol or iodine (1 in 8); chrysarobin (2 in 24); sulfur or tar (1 or 2 in 8); and phenol (1 in 20) are useful.

R. Sabouraud recommends stimulating affected areas with a brush several times a day after applying the following preparation:

℞ Olei cadini (deodorized)		
Olei olivae	ãã 1 ounce	30 cc.

The following prescription is very helpful:

℞ Balsam of Peru	0.5 dram	2 Gm.
Sulphuris praecipitati		
Betanaphthol	ãã 1.0 dram	4 Gm.
Petrolati	q.s. 1.0 ounce	30 Gm.
M.S. Rub into affected areas twice daily.		

Croton oil, chrysarobin and pyrogalllic acid have been used on the assumption that they produce follicular suppuration and thus hasten recovery.

Roentgen irradiation of tinea tonsurans is beneficial if given by an experienced roentgenologist. Occasionally a patch may be epilated by a single roentgen treatment.

TINEA FAVOSA (FAVUS; PORRIGO FAVOSA; DERMATOMYCOSIS FAVOSA; CRUSTED RINGWORM; HONEYCOMB RINGWORM)

Tinea favosa is a contagious disease produced by the *Achorion schonleinii*, a vegetable parasite. It is characterized by the formation of small, round, or oval, cup-shaped, pale yellow, brittle crusts which are commonly seen about the hair follicles. The hair perforates these lesions. The term "favus,"

signifying a honeycomb, was suggested because of its resemblance to the cell of a honeycomb (Fig. 106).

Treatment.—Destruction of the causative parasite calls for adequate local treatment. The crusts are first removed and the affected areas are treated with a parasitic lotion or ointment to destroy the offending fungus present on the surface and within the hair follicles and hair shaft. Firm crusts are easily removed when saturated for twenty-four hours in oils, of which the oil of ergot is most effective. Olive oil, almond oil and phenolized oil are not suitable. Poultices are



Fig. 106.—Permanent alopecia in a female resulting from tinea favosa.

not only unpleasant but injurious because they stimulate growth of organisms and increase swelling of the epidermis, thus retarding the action of the parasiticide.

Solutions of parasiticides, varying in dilutions from 25 to 50 per cent in boroglycerine, are excellent lotions because of their detergent and antiseptic action. These lotions are sponged over affected areas after the crusts have been removed by soaking them in oil of ergot for twenty-four hours. The crusts can be easily peeled off within one or two hours, leaving the integument in a proper state for the application of parasiticides. Some clinicians prefer naphtholized zinc oleate oint-

ment. The oleates of mercury and copper are beneficial. The following two ointments are recommended:

℞ Hydrarg. oleati unguenti		
Adipis	āā 4 drams	16 Gm.
℞ Cupri oleati	0.5 dram	2.0 Gm.
Adipis	1.0 ounce	30.0 Gm.

The first of these ointments is rubbed into the involved areas with the finger tips. A few days later it is alternated with the second ointment, which is astringent and relieves any irritation set up by the former preparation. These applications are made daily or at intervals of two days and continued for a period of three to four weeks.

Other efficient remedies are a 10 per cent resorcin vaseline ointment, a 10 per cent ointment of boric acid, 5 per cent chrysarobin ointment, 10 per cent thymol iodide ointment, and 5 per cent euophen ointment.

The diseased hairs should be epilated before antiparasitic ointments and lotions are used. Sabouraud has successfully used roentgen rays in favus, but the difficulty of their therapeutic application is the main objection against irradiation.

ALOPECIA AREATA

Alopecia areata is a disease of the scalp and hairy parts of the face in which the hair falls out in patches, leaving smooth bald areas (Fig. 107). It generally appears in early adult life and occurs equally in both sexes. The condition is rare before the age of three years and seldom occurs after the age of sixty. There is a rise in incidence among women between forty and fifty (pelade de la menopause). Several cases have been reported among women after ovariectomy and among men after castration.

The disease is probably of inflammatory origin, although its etiology is obscure. It is believed that neurogenic factors play a rôle in the etiology, since injury to certain nerves produces patches of baldness in areas supplied by the injured nerves. Psychical disturbances, such as anxiety or worry, are also predisposing factors. Reflex irritation is regarded by some clinicians as a causative factor. Falling of the hair is always the result of inhibition of function of the hair papillae

due to disease or to destruction of the nerves supplying them. Cases of universal alopecia following severe mental disturbances appear to support this view.

Some clinicians believe that alopecia areata is due to local infection. The foci of infection in this case are usually found about the teeth, tonsils and sinuses. The condition may also be a sequel to an acute infection, such as erysipelas, influenza, pneumonia, or mastoiditis. Some believe it to be an allergic condition, while others consider it an endocrine sympathetic disturbance.



Fig. 107.—Nineteen-year-old male with alopecia areata.

Symptomatology and Prognosis.—Alopecia areata may be associated with scleroderma, leukoderma, Graves' disease, pregnancy, lupus erythematosus, or lead poisoning. The disease may be of sudden or gradual onset. In some cases a large circular patch of baldness appears over-night. In these instances the integument is usually pink and edematous. Neuritis may also be present in these cases. Pain is often an accompanying feature.

The patch of baldness usually starts as a small area and

gradually enlarges. Several patches subsequently appear, which may lead to considerable loss of hair. The hair of the beard, eyebrows, axillae and pubes may be involved. In severe cases the entire hair of the body, including the eyelashes, is shed (Fig. 108).

The hair of the scalp is completely lost, leaving a band of hair extending from ear to ear around the periphery of the cranium, in one form of alopecia areata.

The patches are characteristic in the patchy form of alopecia areata. The center of each patch is as a rule completely



Fig. 108.—Alopecia universalis. Note absence of hair of eyebrows and eyelashes.

bald. Surrounding this bald center a few stumps of hair are evident. These hair stumps are club-shaped, so called "exclamation-mark hair," becoming thicker as they move away from the scalp.

The hair does not break as in cases of ringworm of the scalp whenever an individual hair is pulled. Stippling or cribbing of the finger nails is often an accompanying feature (Fig. 109).

The prognosis is unfavorable in generalized forms of this disease, but favorable in the more localized forms. The new

hair which appears in the localized form of alopecia areata is usually white, becoming pigmented when it is replaced by further new growth of hair. The prognosis of alopecia areata is good in individuals in whom the eyebrows or eyelashes are present, but very bad in patients in whom they have disappeared. Complete recovery in cases in which the finger nails are cribbed is rare.

Treatment.—Treatment is immediately instituted whenever the diagnosis of alopecia areata is made. Agents which stimulate hyperemia of the affected areas are indicated. The patches are painted with pure phenol, iodine, or turpentine.



Fig. 109.—Note cribbing of nails which is often present in alopecia areata.

The high frequency current and the daily use of ultraviolet radiation are of value. Foci of infection are eliminated and tonics are indicated. Glandular therapy, in the form of whole pituitary gland, suprarenal cortex, or whole thyroid gland, is occasionally of value in the treatment of this condition.

R. Sabouraud recommends the following preparation in the early stage of alopecia areata.

R. Acidi acetici glacialis	2.5 drams	10 Gm.
Formaldehydi	15.0 minims	1 cc.
Aquae cologniensis	q.s. 10.0 ounces	300 cc.
M.S. To be applied daily with a stiff toothbrush.		

In more serious or advanced cases he advises the following ointment:

R Deodorized olei cadini	2.5 drams	10 Gm.
Turpeth mineral	15.0 grains	1 Gm.
Vaseline	2.5 drams	10 Gm.
Adipis lanæ	2.5 drams	10 Gm.
Oil verberna	q.s. 15 gtts.	1 cc.

M.S. This ointment is applied every night in cases of men and the scalp shampooed the following morning.

It is applied three times a week in the case of women, and the scalp shampooed once a week.

R. Sabouraud considers the following topical application the best medication. The objection against this preparation is the fact that it stains the integument:

R Acidi chrysophanici	1 ounce	30 Gm.
Chloroformi	1 ounce	30 Gm.

M.S. To be applied daily until a marked local sensitivity of the skin results and the integument assumes a mahogany color.

ALOPECIA PREMATURA

Alopecia prematura generally appears in males about the age of twenty. The causes of this malady are heredity and seborrhea, of which heredity is important because it is the usual etiologic factor in individuals in whom complete baldness appears at an early age.

The course of alopecia prematura may be slow or rapid. Its progress is sometimes delayed by the temporary appearance of lanugo hair about the temporal regions before the stage of complete baldness is reached. Complete baldness in alopecia prematura resembles the senile form of alopecia with its smooth, shining scalp. Grayness seldom precedes alopecia prematura.

The progress of this condition can be checked under suitable therapy. The lanugo hair usually preceding its onset may be replaced by normal hair. Total alopecia is occasionally the end result of alopecia prematura. While the crown may in some instances be completely denuded of hair, a wide band of hair may persist about the periphery of the scalp.

Treatment.—A period of at least six months of continuous treatment is necessary for recovery. Seborrhea is corrected whenever present. Tight-fitting hats are discarded. Certain drugs, such as pilocarpine, camphor, chloral hydrate and cantharides, are employed for their stimulating effect.

A fifteen-minute massage of the scalp each day followed by ultraviolet irradiation is about the best mode of treatment. The scalp is anointed with vaseline before commencing each treatment.

ALOPECIA SENILIS

Alopecia senilis is commonly seen in males between the ages of forty and fifty years. Its approach is usually preceded by grayness. The condition is always symmetric and the af-



Fig. 110.—Senile alopecia in a male, seventy years of age.

affected areas are covered with smooth integument. The hair follicles are not dilated. Loss of hair commonly appears on the vertex and temples. This condition is incurable (Fig. 110).

SYPHILITIC ALOPECIA

Syphilitic alopecia occurs during the secondary stage of syphilis. It has certain pathognomonic features. The condition as a rule occurs during the third month of the disease, corresponding in time to the appearance of the roseola. The onset may be delayed until the fourth month, but very rarely until the sixth month of the disease.

Shedding of the hair is sudden and is at first diffuse. Small areas denuded of hair suddenly appear in the temporal and

occipital regions. The whole scalp presents the so-called "moth-eaten" appearance. This is the "alopecie en clairieres" of the French and is very characteristic of syphilis. Syphilitic alopecia does not result in complete baldness.

Falling of the hair is continuous for a period of three weeks. Spontaneous growth of hair occurs without treatment. A similar and characteristic shedding of hair of the eyebrows is usually present in case of syphilitic alopecia.

CICATRICIAL ALOPECIA

Two forms of cicatricial alopecia are recognized:

1. Congenital cicatricial alopecia is a very rare anomaly resulting from adhesions of the fetal membranes to the scalp.
2. Acquired cicatricial alopecia may be due to any condition which destroys the hair follicles. Of these conditions mention is made of wounds, burns, prolonged roentgen irradiation, suppuration of the hair follicles, syphilitic ulceration of the scalp, lupus erythematosus, favus, etc.

Acquired cicatricial alopecia is known as "folliculitis decalvans." The condition is characterized by the appearance of split-pea, dime, or palm-sized patches of progressive folliculitis which produce considerable scarring and end in permanent alopecia. The lesions may be few or numerous. These lesions often coalesce to form larger ulcerated areas, leaving a few tufts of hair scattered over the scalp. The hairs which are not shed are usually normal in appearance. However, some of these hairs may be easily epilated, revealing a succulent, white glossy sheath. The integument within the patch is white, smooth and atrophic. Some of the hair follicles found at the borders of these patches are inflamed. The degree of this inflammation varies from pustulation and crusting (folliculitis epilante Quinquaud) to a scarcely perceptible rosy tint (pseudo-pelade de Brocq).

The prognosis is unfavorable. The disease tends to progress slowly, although spontaneous arrest may occur. The hair never grows on the affected areas.

Treatment is of little value. Epilation of the hair at the periphery of patches where the follicles are inflamed has been advised. Inunctions of antiseptic ointments containing mercury or sulfur may be helpful.

Diffuse Falling of the Hair.—This may occur without the accompaniment of disease of the hair or scalp. The most common cause of this type of falling of the hair is probably the presence of fever. R. Sabouraud observed that diffuse falling of the hair accompanied fevers above 39° C. (103° F.). He is of the opinion that it does not occur unless this temperature is reached, regardless of how long a lower temperature continued. The hair in patients running a temperature of 39° C. (103° F.) or more begins to fall from two to six weeks after the onset of this high fever.

Loss of hair may also follow surgical shock, childbirth, or miscarriage. There is also a certain amount of loss of hair following the menopause and in old age. Debilitating diseases producing premature senescence are factors which cannot be overlooked.

The *treatment* of diffuse falling of the hair in the absence of diseases of the scalp or hair is directed to the improvement of the general health of the individual and stimulating the circulation in the scalp. The exposure of the entire body surface as well as the scalp to ultraviolet irradiation is of benefit.

The employment of mechanical or electrical agents for improving the circulation in the scalp is always helpful. Local medication is of doubtful value.

GENERAL CARE OF THE SCALP

Washing the Hair.—Women wash the scalp once a week or once a month, and whenever they seek the services of the hair-dresser. Men, on the other hand, wash the scalp daily, or once a week.

Frequent washing of the scalp is not so necessary as is usually assumed as long as the hair is brushed and combed at regular intervals. The scalp is rarely washed in tropical countries where the hair of the women is remarkable for its luxuriance, length and gloss. It is injurious to have the hair constantly moistened. No harm results whenever the hair is properly dried. The least possible friction is applied whenever the hair is dried, because moistened hair breaks more readily than dry hair. It is necessary to cleanse the hair more frequently when it is thin and oily than when it is coarse and dry.

Most women living and working in the dirty city atmosphere clean their scalps monthly. A lather of soap and hot water is sufficient for this purpose. A fat-free soap is preferable on account of its low content of free alkalis. Washing the hair with soft water, such as rain water, gives the hair a beautiful gloss and frees it from deposits. Shampoo powders should be employed whenever the water is hard. These powders contain powdered soap, a small amount of alkalis, and borax. Tincture of Quillaia (a natural soap obtained from tree bark) is the essential base of "dry shampoo." It is an excellent material for cleaning the scalp. Salt water bathing does not injure the hair. Rinsing in soft water is necessary after sea-bathing on account of the stickiness of salt water and to eliminate the sodium chloride present. The whipped white-of-egg is an excellent adjunct for shampooing; it makes the hair very glossy. It is applied to the scalp and rinsed off with soft, warm water. The yolk of egg should be avoided because it adheres to the hair and its removal is more difficult.

The use of powders provides another method for shampooing oily scalps and long hair. The scalp is well dusted with potato starch or plain talcum powder. The excess is removed by brushing. Tar soap is preferable for the shampoo in individuals with dry scalps. Sulfur soap is beneficial in individuals with oily scalps.

Dull Hair.—This results usually from insufficient brushing or combing or from the very frequent use of the "permanent wave." Invariably the hair looks dull a few days after a "permanent wave" has been applied. This can be avoided by using an oily lotion at least one hour before visiting the hair-dresser.

Dry Hair.—Dry hair usually results from frequent washing of the scalp, or from employing lotions containing alkalis or alcohol.

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CONSTIPATION

THE commonest of all gastro-intestinal conditions is constipation. Perhaps the simplest definition of this condition is a failure in colon function. Whether that failure be partial or complete, involving the colon proper or its most distal portion the rectum, constipation requires the serious thought of every thinking physician.

I know of no authentic figures, but nearly half of the population are so afflicted. Although the world's literature is replete with information on this subject, most of it is absolutely valueless. There are volumes which would attribute everything, from headache to flat feet, to constipation. The student of this subject can find in the literature an immense amount of data dedicated to the belief that intestinal toxemia is the cause of all human ills. Not a few of the human race have lost their colons in the firm belief that colectomy was a panacea but, like all other movements, under the sobering influence of time the epidemic of colectomies has ceased and the enthusiasm of the authors has waned.

The activities of an amazing number of microorganisms and a clearly alarming group of symptoms and signs are associated with this condition. On the other hand, serious thoughtful study of the subject emphasizes how little we know regarding the exact status of this affliction. We know, from a clinical angle at least, what failure in elimination on the part of the bowel will do, but we are in need of an unbiased, clean-cut study of this subject. There is now little doubt that delay in the terminal colon exerts a very different effect from delay in the head of the bowel. There seems to be no reason to dispute the fact that defective colon evacuation can result in far flung toxemia and probably produce, and always aggravate, any existing cardiac, renal, hepatic, digestive, circulatory, or

nervous condition which may exist. Just what form of toxin, what form of bacteriology, is responsible is not always clear, but very gradually we are seeing the light.

What is equally important is the fact that the great bulk of the lay public are slaves to various habits: the drug habit, cathartic habit, dietary fads and fancies, the use of such and such a meal, and the use of colon filling stations which flourish over the length and breadth of our land. There are innumerable laxative preparations on the druggists' shelves. Millions are spent on food propaganda, nostrums for constipation, and ridiculous suggestions regarding vitamins—regardless of whether the constipation is due to bad habits, carelessness, or perhaps organic disease like partial obstruction or cancer.

Today, we have at our disposal means for determining the type and usually the cause of constipation. Constipation is an individual problem, and the only way to curb the pernicious action of some corner druggists and some of the obscure propaganda scattered through periodicals and by radio is to make the individual realize that only a careful study of each case will determine the cause and nature of the problem and the satisfactory form of treatment. If the public would realize the danger of attempting to fool with one of the most important organs they possess, they would no more use inexperienced management for that purpose than they would let a hammer-and-chisel mechanic work on their automobile engine. Equally culpable are medical men who dismiss constipation with a nod and a prescription when a careful study is indicated. I propose to discuss this subject as simply as possible.

CAUSES OF CONSTIPATION

The enclosed list is modified from that of Gant. It will serve our purpose admirably because it represents, in a sense, those subjects which we have to bear in mind in regard to constipation. Let us discuss them for a moment:

There seems to be no reasonable doubt in the minds of most physicians that there is an hereditary basis for some constipation. It seems to me that much more likely is the type of habitus which predisposes to the condition. I have repeatedly seen visceroptotics in whom a simple form of constipation was seen in several generations. Perhaps the correct explanation might be the fact that the succeeding generation

enhances the hereditary factor of the former. Sex is likewise a predisposing cause, women being far more frequently subject to constipation than men. Menstrual periods and pregnancy do much to alter the tonus of the visceral nervous system, and irregularities at those periods are frequently forerunners of habits.

A little thought taken seriously in the direction of occupation reveals many things which predispose to constipation: irregular habits, scanty meals, and long hours are encountered in any number of occupations in which constipation should flourish. Chronic invalidism by enforced lack of exercise, general muscular impairment and sedentary existence account for another large number; impairment of the abdominal muscles, whether due to utter flaccidity or following pregnancy or due to abdominal operations, must likewise contribute a number. One could illustrate these without number. It is only necessary to bear constantly in mind these larger predisposing causes.

Diet.—Perhaps more directly apparent are the determining causes. The first is the diet. In ordinary functional constipation the physician should carefully survey the dietary regimen of the individual. Any number of faults are to be found in this arrangement: 1. An unbalanced dietary, a lack of substances with a sufficient residue, a lack of the fresh vitamin-containing foods, the habit of eating irregularly or of eating one very large meal, the habit of eating too much of one variety of food, puts too much of a strain on the digestive tract and results in fatigue of the muscles. All of these, when present, demand a serious revision of the diet and an attempt at regulation along these lines. 2. Habits, next to the necessity for a regulated dietary, are just as essential as proper fuel for an engine. The habit of disregarding the call to stool until it becomes imperative has been the forerunner of many cases of constipation. Catching a train, hurrying after the morning meal, lack of improper toilet facilities, false modesty in public places (which can all be summarized by the statement that there is no regularity in habits), explains many of the cases of functional constipation. Toilets should be low, rather than high, in order that the flexion of the thighs on the abdomen will be of value in permitting satisfactory evacuation. A little thought to these things and the necessity for impressing these

things, especially upon the school children, selecting if possible an appropriate period, preferably after breakfast, is a vital need.

Drug and Enema Habits.—Nearly every individual who complains of constipation has established some habits, all the way from laxatives, purgatives, and cathartic drugs, to salines and various enemas. Nearly always there is a gradual tendency to increase the strength of these substances, and there are few drugs which can be used without harm; nearly all of them can bring about dysfunction and induce colon pathology. Whenever an individual takes saline laxatives I expect to find, with the sigmoidoscope, a red, inflamed bowel wall. The enema habit, unless regulated by the physician, is equally guilty of producing the same effect.

These substances should be made to fit the case, but the ignorant individual seizes upon the drug method which has succeeded with Mrs. So and So, hardly realizing that her problem is perhaps a very different one. This is not the place to discuss the irritating effects of various drugs and chemicals. Many chemicals likewise have a bad effect on the bowel. Astringents, such as copper, alum, iron, and lime salts (which are occasionally in food or drinking water), and lead and bismuth (the former among painters), are likewise responsible irritants.

Inflammation of the Bowel.—An inflammation of the colon is as common as sore throat and chronic inflammations of the head. This fact has not yet penetrated average medical opinion in spite of the works of Schmidt, Coombe and others. Only those of us who are accustomed to examining the interior of the bowel endoscopically and studying the x-ray picture as well as the analyses of the stools can realize how frequent this is. I have no hesitancy in saying that a very large number of cases of constipation are in reality colitis, sigmoiditis and proctitis and that in many instances the bowel wall is infected.

Functional Causes.—Another category of determining causes are the two great functional groups, described as *spasm* and *atony*, or spastic constipation and atonic constipation. In the former the tonus of the distal colon is markedly increased and the phenomena which dominate the picture are those of spasm. One feels the spastic sigmoid through the abdominal wall and notes the spastic bowel frequently by digital palpa-

tion. The narrow calibre of the stools is characteristic and this is the type most frequently seen with the whole group of colon inflammations. The atonic bowel presents none of these appearances but is lazy, relaxed and muscularly inefficient.

Psychic Causes.—One of the most interesting observations which every gastro-enterologist of experience must have had is the marked dependence of the left colon on all sorts of impressions. A nervous diarrhea has been described and recognized but, to my mind, more common than this is the behavior of the left colon in the direction of spasm. Fear, anger, grief, and even joy—in fact all emotional shocks—may in a sensitive individual bring about this result. Less apparent and perhaps more effective are those causes of common neuroses, namely, maladjustment, frustration, and fear which in this modern world play so large a rôle. I am more and more impressed with the sensitiveness of the distal colon, not only to conditions within the digestive tract, but to emotional disturbances as well. Some have assigned the most sensitive part of the digestive tract to the pyloric sphincter. I am inclined to call the left bowel the *Prima Donna* of the digestive tract.

Obstructive Causes.—If all forms of constipation could be explained on the data which we have already presented, the problem would be simple. Unfortunately, the dangers and the severe types of the condition are frequently associated with true obstruction. It is our problem as medical men, in every instance of constipation to rule out this possibility before proceeding with therapy. We have the means for thoroughly studying the bowel by means of x-ray and sigmoidoscopy. It is well to discuss for a few moments the obstructive causes of chronic constipation so that we can bear them in mind and rule them out in any given case.

Congenital Deformities and Displacements.—Today we realize that the form and position of the bowel are largely a question of habitus. A large proportion of the human race has an asthenic habitus, with organs which are relatively low in position and yet these organs functionate normally. If we study the embryology of the colon it is not difficult to realize that many alterations can occur before complete rotation and fusion permit the bowel to be in what we consider the normal position. Congenital anomalies, such as narrowing of the anus or total absence of rectum, or imperforate anus or rectum,

scarcely ever come to our attention because they are usually handled surgically early in life.

Acquired Deformities and Displacements.—This is most frequently seen in the group which we call visceroptotics. It is necessary to realize that many of the deformities are acquired. They are due to stasis, weakness or the muscular atony after severe illness, displacements occur or become more pronounced and, if local inflammation involving the peritonarium occurs, adhesion formation, fixation, deformity and kinking may follow. Any number of varieties of this process are possible. They are recognized by careful x-ray examination under the screen. This procedure enables us to determine not only the form and position of the bowel, but also the degree of mobility so that adhesions may be recognized by abnormal fixation of the gut.

Extraintestinal pressure is not uncommon. Abdominal tumors and masses, pelvic tumors, displacements of the uterus, an enlarged prostate, and pregnancy account for such pressure. These must be constantly borne in mind so that in every case of confirmed constipation a pelvic examination is necessary. Fixation of the colon by adhesions and pressure from the same type of condition are exceedingly common and will frequently explain the inability to relieve ordinary constipation by medical therapy.

Strictures may be benign, ulcerated, or neoplastic. They may come from within the bowel wall from a stenosing ulcer, syphilis, tuberculosis, or an annular carcinoma which is the serious organic lesion which we fear. Most of these are readily recognized by radiographic studies.

Angulations may be congenital or acquired. They are most frequently seen in the sigmoid, with its long mesentery, at the termination of the ileum owing to a downward prolapse of the cecum. Many forms of angulation are recognized in the transverse colon and occasionally in the ascending colon. In a marked general prolapse of the viscera the right colon suffers most, the cecum going into the pelvis, the hepatic flexure being frequently opposite the iliac crest, while the splenic flexure, which most frequently resists descent, may become acutely angulated.

Adhesions are one of the most fertile sources of constipation, not only fixing the bowels, but frequently obstructing the

bowel. They are most frequently seen following operations and, in my experience, there are four cardinal sites: The commonest are adhesions in the lower right quadrant, most frequently due to appendicitis with drainage. In the upper right quadrant, gallbladder surgery is most responsible. While fixation of the duodenum is the most common aftermath, one not infrequently encounters adhesions to the hepatic flexure and the transverse colon. Central incisions, often due to gastric surgery, more frequently involve the small bowel but may involve the colon. Suprapubic incisions for various pelvic diseases most frequently involve the sigmoid and they are probably the most difficult to satisfactorily detect on the fluoroscope. Adhesions from serious forms of enterocolitis in childhood can produce widespread deformity. At this point it is well to mention the abnormal mesentery.

Normally the cecum can be moved under the screen for a distance of about 3 inches. Abnormally it may be moved over twice this area, bringing about the so-called "cecum mobile" which is usually associated with high constipation. The sigmoid flexure may bring about all sorts of situations and have one or two loops with a mesentery so long that partial twisting or even volvulus is not uncommon.

Among the causes of chronic constipation which must be considered are *volvulus*, *intussusception*, and *hernial orifices*. Volvulus occurs most frequently at the junction between the fixed and movable portion (the sigmoid) and next in frequency is the cecum, and a quarter or half twist may bring about partial obstruction and obstructive constipation. Two things must always be borne in mind in volvulus: (1) the possibility of an abnormal, large mesentery, and (2) the danger of adhesions. Invagination or intussusception occurs most frequently at the ileocecal valve, then in the ileum, third in the jejunum, and fourth in the colon. A tendency to abnormality in the mesentery may permit the ilio pelvic colon to invaginate in the upper part of the rectum. The recognition of a mass, bloody stools, and the acute phenomena of obstruction may make the diagnosis of an acute invagination. Chronic forms bringing about severe constipation are only recognized by careful physical and x-ray study.

Foreign bodies include gallstones, hair balls, enteroliths, coproliths, and even pancreatic, urinary and prostatic calculi.

Worms have produced the same effect. While most of these are interesting clinical curiosities, a survey of the literature demonstrated that they are not uncommon. Far more common, however, is fecal impaction which must be discussed separately.

Diverticula.—These are very common and may be found over the entire colon; more frequently they are in the distal segment of the bowel or in the sigmoid. Prodiverticulosis, diverticulitis, and peridiverticulitis are now well known clinical entities, recognized on x-ray examination as exceedingly frequent and in many instances explaining a rather severe constipation. You may surmise their presence, but the exact diagnosis is made by x-ray study. Occasionally sigmoidoscopy may reveal their orifices. It is necessary to realize their importance and recognize them because they call for a special method of treatment.

Paralytic Ileus.—This is a dangerous condition. It may be found in very severe illness, but it is most frequently seen following trauma to the bowel, mechanical handling or injury, or nerve shock. In this condition the function of the colon has been arrested. No further progress of material occurs, and there is stagnation and bacterial proliferation. The formation of toxins and absorption bring about a severe picture, and yet we see a static bowel not unlike some of these conditions in ordinary medical work.

Dilatation of the Colon (Congenital Megacolon and Hirschsprung's Disease).—As a rule this is a congenital anomaly, with marked abdominal distention, anemia, malnutrition, and even ulcerative colitis. It can be suspected in infants or very young children from the general contour of the abdomen and the diagnosis is made certain by x-ray study.

Fecal Impaction.—This may occur at any part of the colon. While it is most frequently in the rectum, adhesion formation or new growth may cause a severe impaction above that level. It must be remembered that impaction can occur in the cecum and ascending colon as well as in the rectum and one of the most severe cases that I have ever seen resembled a hard nodular mass in the right iliac fossa. In every case of chronic constipation digital examination is indicated to rule out this possibility in the rectum.

Equally important are the *rectal causes* for constipation. In a very large number of cases these explain the condition: spasm of the sphincter, fissure or hemorrhoids, new growths, ulcer and inflammation. Many confine their study to examination of the rectum, visual inspection, digital examination and proctoscopy, and it is true that many cases can be explained in this way; but it is our duty to cover the entire problem if we expect to reach a high degree of success.

There are two points which ought to be mentioned before this phase of the subject is dismissed. One is the necessity for constantly bearing in mind, particularly with progressive constipation and weight loss, the possibility of carcinoma of the bowel, if for no other reason than to rule out this lesion. The other is the importance of spasm. As I have already mentioned, spasm gives a rather characteristic x-ray picture, rather characteristic physical signs, a rather characteristic stool, and can produce the same obstinate type of constipation. Furthermore, in my experience it is by all odds the most chronic type of constipation.

SYMPTOMS OF CONSTIPATION

There may be only irregularity or incompleteness in bowel evacuation, engendering abnormal function.

[illegible]

Worms have produced the same effect. While most of these are interesting clinical curiosities, a survey of the literature demonstrated that they are not uncommon. Far more common, however, is fecal impaction which must be discussed separately.

Diverticula.—These are very common and may be found over the entire colon; more frequently they are in the distal segment of the bowel or in the sigmoid. Prodiverticulosis, diverticulitis, and peridiverticulitis are now well known clinical entities, recognized on x-ray examination as exceedingly frequent and in many instances explaining a rather severe constipation. You may surmise their presence, but the exact diagnosis is made by x-ray study. Occasionally sigmoidoscopy may reveal their orifices. It is necessary to realize their importance and recognize them because they call for a special method of treatment.

Paralytic Ileus.—This is a dangerous condition. It may be found in very severe illness, but it is most frequently seen following trauma to the bowel, mechanical handling or injury, or nerve shock. In this condition the function of the colon has been arrested. No further progress of material occurs, and there is stagnation and bacterial proliferation. The formation of toxins and absorption bring about a severe picture, and yet we see a static bowel not unlike some of these conditions in ordinary medical work.

Dilatation of the Colon (Congenital Megacolon and Hirschsprung's Disease).—As a rule this is a congenital anomaly, with marked abdominal distention, anemia, malnutrition, and even ulcerative colitis. It can be suspected in infants or very young children from the general contour of the abdomen and the diagnosis is made certain by x-ray study.

Fecal Impaction.—This may occur at any part of the colon. While it is most frequently in the rectum, adhesion formation or new growth may cause a severe impaction above that level. It must be remembered that impaction can occur in the cecum and ascending colon as well as in the rectum and one of the most severe cases that I have ever seen resembled a hard nodular mass in the right iliac fossa. In every case of chronic constipation digital examination is indicated to rule out this possibility in the rectum.

The above symptoms have been suggested for constipation. You can take your choice and the list can even be enhanced further. Ordinarily, the first symptom is irregularity or insufficiency in bowel action. This is the first thing that the patient complains of. The second significant thing is the fact that a symptom or symptoms such as lassitude or indigestion rather noticeably improve when the bowels act. The patient quickly learns to use druggist's therapy and to proceed with this therapy until the obstinacy is such as to demand investigation. It would be folly to discuss these various symptoms. All of them, and in fact all diseases, can be associated with the symptom of constipation. The only interesting point, from the standpoint of medical treatment, is the fact that treatment directed toward constipation results in subjective well-being and an improvement or disappearance of many of these signs.

DIAGNOSIS

The diagnosis of chronic constipation demands a careful survey of the individual, which can be briefly outlined as follows:

The History.—This demands an investigation as to the cause preceding and precipitating the condition. All of those things which we have mentioned under causes are pertinent in this connection. Most important, to my mind, is a survey of the individual dietary. We should ask our patients exactly what they eat, when they eat, and how much they eat. You can frequently put your finger on the problem right there. The question of regularity in bowel habits is equally important and obvious. Another point is the use of drugs and enemas. A patient who has been using heavy salines may be expected to have colitis. The same is frequently the case with other drugs: enemas, particularly watery enemas, and the use of large amounts of fluid in the bowel—3 to 6 quarts are not only to be condemned but are positively dangerous. Previous inflammations of abdominal organs, and most important a knowledge of previous operations and possible adhesion formation, must all be ascertained.

Physical Examination.—This includes inspection for undue distention, the presence of scars, possible tumors, palpa-

tion of the colon (especially in the ascending and descending portion) and, where possible, the determination of tenderness over the colon and the demonstration of any mass (whether due to neoplasm or fecal impaction).

Stool Examination.—This is routine in all cases. It gives the picture of digestive work. The presence of undigested food may suggest trouble high up in the stomach, biliary tract, pancreas, or small bowel. Fresh pathologic elements in the stool, notably mucus, pus, blood, and cellular elements, particularly if on the outside of the stool, or following the stool, and the demonstration of parasitosis are of importance. It is hardly necessary to point out the value of blood or the importance of pus in blood in chronic cases as indicating ulcerative colitis or carcinoma.

Digital Examination.—This is to demonstrate the direction and the presence of gross lesions of the rectum and is followed by proctoscopy and sigmoidoscopy for directly inspecting the lower distal colon. This enables one to make a direct diagnosis of many lesions: ulceration, hemorrhoids, fissures, hypertrophied valves, cryptitis, proctitis, sigmoiditis, catarrhal inflammations, infection, ulceration, and new growth. This method of study is indispensable and sigmoidoscopy may give a clue to the whole bowel picture.

x-Ray Examination.—This of course is a study of the bowel from two angles, and first of the function of the colon as shown by the demonstration of the opaque meal by mouth. We can determine in this way the point of delay, the nature of the intestinal contractions, and establish certain types of constipation. In the ascendens type, nearly all of the barium meal is in the right colon. In the atonic type it may be distributed throughout the bowel but, forty-eight or seventy-two hours later, there is no visible attempt at evacuation. In the spastic type the entire left colon may show no barium, or barium mixed with mucus may produce a long string-like shadow of the descending colon and sigmoid so characteristic of spastic colitis. Spasm not infrequently involves the transverse portion of the bowel as well. Finally we have a rectal type of dyschezia in which the arrest is obviously in the rectal ampoule. This is of course also recognized by digital examination.

Apart from this study no x-ray study of the colon is complete without the opaque enema. This should always be preceded by a thorough cleansing of the bowel, either with castor oil or with multiple enemas. In this way we can fill out every inch of the colon, seeking to demonstrate a fixed organic defect. This is the most satisfactory way of demonstrating a new growth, changes in calibre or outline of the colon. Any disease which alters the outline or contour, and this includes stricture, adhesions and particularly new growths, can be demonstrated in this way.

The gastro-enterologist who has experience with this method of examination will be repaid by such study. Where he is not so informed he should have the services of a trained roentgenologist. In this way he can rule out or demonstrate organic colon disease, which after all is the first and most important thing to do in any persistent progressive case of constipation.

TREATMENT OF CONSTIPATION

The treatment of constipation depends upon the analysis of the condition which has been made. If such an analysis reveals some obstructive cause, then obviously the only solution of the problem will be either correction of the cause or some adjustment by which the cause can be surmounted. In many forms of obstructive constipation the obstruction is only partial and has existed for many years. This is particularly the case with the adhesion variety, with kinks and visceral displacements, in which there is either stasis or simply a local delay. In these cases it may be necessary to use local measures, those directed toward the rectum and sigmoid being the most successful.

Where possible conditions like fissure, intractable hemorrhoids, and sphincter spasm exist, they ought to receive local treatment, either by dilatation, divulsion, or removal. The necessity for operations on the bowel, such as colopexy, entero-anastomosis, and partial colectomy, in my experience is relatively rare because visceral displacement is usually more or less universal and not alone confined to any one segment of the tract. In these cases it becomes necessary to readjust the life of the individual and, if possible, to increase nutrition.

Ordinarily, however, the treatment of constipation, par-

ticularly of the functional type, has been in the following categories:

Re-education.—This has to do particularly with habits. Habits of bowel evacuation, regularity in methods of living, and all those measures of persuasive psychology which have for their purpose the induction of a regular method of living in which time for, and a place for, bowel evacuation is definitely provided.

Correction of the Diet.—In my experience the sluggish nutrition, sedentary type of constipation calls for a diet in which roughage plays an important part: the leafy vegetables, the use of fruits, and the use of whole-wheat rather than white flour. There are any number of substances on the market which are supposed to accomplish this effect. Some are satisfactory but, as a rule, no one type is equally successful in all cases. On the other hand, when there is tenderness, abdominal pain, mucus in the movements, evidence of inflammation, particularly of the distal colon, or the so-called type of spastic bowel, I believe, along with many other men who have studied this condition, that the bland type of dietary is best adapted to these cases in which practically all those irritating and stimulating substances are removed.

Medication.—Regardless of those individuals who believe that all the world can do without medication to the bowels, I feel that a well-ordered medical routine is one which we should all possess. It is well to bear in mind the nature of drug action insofar as the treatment of constipation is concerned. Most pronounced is the fact that no one drug has a specific action, but that most frequently combinations of these substances are more likely to produce satisfactory results.

Exercise.—All medical opinions are in an agreement that moderate exercise is of great value in arousing peristalsis and in properly promoting this action. This includes everything from getting awake in the morning to walking, running, golfing, horseback riding, rowing, swimming, tennis, gymnastics, and bowling. So-called systems of medical gymnastics, properly formulated, setting-up exercise, the use of pulleys, all have their ardent advocates in the handling of this condition. For many years I have been an advocate of the Glenard system which is exceedingly simple and which was outlined under

x-ray control. It is worth trying in these cases. The important thing about exercise is first, regularity, and secondly, a well defined program which must be adhered to.

Hydrotherapy.—This can be divided into the *internal* type, which is water drinking by mouth, the use of enemas, or intestinal irrigations. In Europe, the taking of certain laxative waters is fashionable. In this country the taking of fairly large amounts of water and the use of substances which contain the essential ingredients of most of the laxative waters is just as satisfactory. I personally prefer some combination of the Bourget formula which can be modified to suit the individual and is usually taken hot the first thing in the morning. Where there is rectal retention, I use enemas, either sweet oil or medicated enemas. The quantity of these enemas is specified as well as the frequency with which they are used. Intestinal irrigation is used for its chemical effect to unload and cleanse the bowel. I always insist on preceding the irrigation with an oil injection and following it with a hot flaxseed poultice in order to avoid intestinal reaction. The technic for these procedures will be found elsewhere.

External hydrotherapy consists in the use of various baths, douches, compresses, and packs such as are found so beautifully illustrated in many of the sanatoria. That any and all of these procedures may be of great benefit goes without saying. That the average physician has at his disposal such an equipment is another matter. In many of the larger cities, however, measures of this type can be satisfactorily carried out.

Massage.—*Effleurage*, *pétrissage*, and friction are of great value, especially with invalids and those who are exhausted and toxic. In the dilated, relaxed, nonsensitive colon frequently encountered in older people, mild rotary massage over the cecum and right bowel is of great benefit.

Mechanical Vibration.—This varies all the way from the use of the hand machine to the larger machine (like the Zander apparatus), to the mechanical horse which will produce severe vibration. I have always felt that their use ought to be somewhat guarded, particularly in those cases in which there is undoubtedly a low-grade inflammation.

Electricity.—Constipation in the hands of so-called "elec-

trical specialists" has been treated with practically all varieties of electricity: faradic, galvanic, static, high frequency, sinusoidal, and Morse waves. In the hands of those who have devoted their attention to this subject, the claim is that these measures are of great benefit. I confess that my interest has been spasmodic. Many years ago I was interested in this subject. I realize that the so-called electric enema, such as is practiced in France and which I frequently saw of benefit, and the use of the Morse wave, if delicately handled, are often of benefit. The average physician is not sufficiently trained to achieve the best results with this method of therapy.

Local Treatment to the Rectum.—This consists of dilators and medicated suppositories.

Other Methods of Treatment.—Apart from these measures there are three types of treatment which have engaged the attention of medical men within recent years: The first is the use of *bacterial treatment*, the idea being that it is possible to bring about a change in the flora of the large intestine by treatment directed both toward the diet and to the implantation of certain organisms. Perhaps the most successful of these is the *Bacillus acidophilus*. It is now obtained in cultures and almost universally as acidophilus milk. This organism, alive, will pass through the stomach and ingraft in the large bowel under proper conditions. A lactovegetarian diet is claimed to be effective for this purpose. Where there is an excess of putrefactive organisms with high retention, the use of acidophilus milk in small quantities, not more than 2 ounces and working up to 8 ounces a day, coupled with a lactovegetarian diet and the use of substances like lactodextrine or Beta Lactose, are capable of bringing about a definite change in the flora of the bowel. The simple addition of lactose to the bowel is not sufficient, even over long periods, to bring about a definite acidophilus flora. The use of fermented milks (Koumiss, Kefir, Yoghourt) has been largely discontinued in favor of acidophilus milk. The same is true regarding cultures of *Bacillus bulgaricus*. It has been suggested to give the culture of the *Bacillus acidophilus* through the duodenal tube and also by rectal installation; the latter I have frequently done, taking the precaution to keep up the proper kind of dietary. Whether these measures are successful or not it is

difficult to say. I am not certain as to the value of rectal installations of this organism.

Another method of treatment is *vaccination* against organisms which are known to be pathogenic. My experience has dealt largely with the non-hemolytic streptococci so constantly found in sigmoiditis. I have seen medical results in this way that were not obtainable in any other fashion. The colon bacillus likewise has been a favorite type of study in constipation. There seems to be no reasonable doubt that there are marked variations in this organism and that some are capable of great harm. I feel, however, that much of this therapy is still in an experimental stage and does not yet deserve attention as a definite method of treatment.

The use of the various mineral waters, such as the Carlsbad treatment and the Vichy treatment, both of which are now available for home consumption, offer themselves as methods which can be applied, particularly in those cases where there is a definite upper digestive disturbance involving the liver or biliary tract. I prefer to work out my own solution of these problems rather than to follow any stereotyped methods.

The last consideration brings us to the use of various methods which have been used for chronic constipation throughout the world. They include the use of *mineral oil*, *bran*, *psyllium seeds*, and *Agar*.

The *laxative remedies* are time honored drugs, like cascara, senna, aloin, podophyllin, compound extract of colocynth, and phenolphthalein, which are judiciously used combined with antispasmodics such as belladonna or hyoscyamus, stimulants like strychnia, and even more drastic substances. There are innumerable combinations of these remedies on the market under trade names but it seems to me the simplest method is to write out a prescription such as the following:

Extract of Hyoscyamus gr. $\frac{1}{12}$
Extr. Rham. Pursh. gr. 1
Fel. Bovis Purefact. gr. 1
Extr. Colocynthidis Comp. gr. $\frac{1}{4}$

Sig.: one capsule to be taken on retiring.

This can be modified in various ways with the addition of vegetable laxatives such as aloin, gr. $\frac{1}{4}$, or resin. podophyllin gr. $\frac{1}{12}$. A stronger effect is obtained by increasing the com-

pound extract of colocynth to 1 grain, whereas milder effects may be readily obtained by reducing the amount of all the ingredients.

Senna is a somewhat drastic purge but a popular one because it acts on the large bowel and, in our studies, on the right colon. It can be used either as leaves or pods, crushed up and brewed as a tea. It is the principal ingredient of most of the teas which are sold for the relief of constipation. The old-fashioned remedy of a mixture of ground-up dates, figs, prunes and raisins, of each quarter of a pound to which $\frac{1}{2}$ ounce or more of dried senna leaves is added, needs no comment. It is a laxative remedy somewhat drastic and providing some bulk. The dose of this substance can be found out only by the trial and error method.

The most popular of all remedies for chronic constipation is aromatic fluidextract of cascara, and the dose can be increased or decreased as the patient feels the need. The average laxative dose is somewhere between $\frac{1}{2}$ and 1 teaspoonful.

The innumerable pills on the market presenting various combinations of the above mentioned substances offer only their combinations and the well-made preparations which are available. The objection to nearly all these substances is that they become habit forming, whereas a remedy is to be sought which must be introduced at the patient's discretion.

Far more popular are those innumerable preparations now available which provide lubrication and bulk. *Mineral oil* is the most popular and undergoes no chemical change in the body. There has been some doubt as to whether it inhibits absorption. When there is a tendency to fecal impaction, with dried out stools, this is a most convenient remedy. It is the most valuable in most forms of partial obstruction and diverticular diseases. Another remedy which is almost as popular is granulated *Agar Agar*; this undergoes no chemical change but has the convenience of retaining water and forming bulky, moist stools. Innumerable combinations of mineral oil and agar exist in emulsified forms, such as *Petrolagar* and *Agarol*, which are fortified with the addition of phenolphthalein. Another preparation contains mineral oil and magnesia. *Psyllium seeds* have been used not only to produce bulk, but because the mucilaginous exudate is soothing and healing to the bowel.

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There is a preparation of mucilage of psyllium seeds without the seeds known as *Parapsyllium*. *Regulin* is a preparation of agar and cascara.

Innumerable combinations of these essential remedies have been prepared and are now available, while newer remedies have constantly appeared. *Coramine* is a popular French remedy of many years' standing with a mucin-like effect. New and effective remedies giving both bulk and retaining moisture in the stools are *Metamucil*, *Mucilose*, *Kondremul* (a mixture of mineral oil and Irish moss), *Mucara*, and *Saraka*. All of these remedies and some which have not been mentioned of this type seek to regulate the bowels by adding bulk and moisture. Those which are not reinforced by laxatives require patience and persistence in their use and occasionally the use of enemas until the habit is established.

In many instances the constipation is so interminably spastic in type that any method will not succeed until the left colon and nervous system is relaxed. The result is that these patients are reduced to the use of transit purges such as saline cathartics and use castor oil in order to promote action of the colon. One European investigator pointed out that if the average person who is chronically constipated persisted in avoiding drugs but followed a well-balanced diet, bowel function would usually be resumed on the third or fourth day. The average person rarely has the patience to persist in such a regimen.

CLINIC OF DR. BENJAMIN HASKELL

JEFFERSON HOSPITAL

THE OFFICE TREATMENT OF HEMORRHOIDS AND OTHER COMMON ANAL CONDITIONS

THE treatment of hemorrhoids will vary with the type of hemorrhoid and with the pathologic changes that have taken place. Symptoms likewise will depend upon the same factors.

The simplest classification of hemorrhoids is based upon their surface covering; an internal hemorrhoid is covered with mucosa and an external one with skin, regardless of their location in relation to the anal canal. The changes that occur in the development of the hemorrhoid will likewise vary with the type. The external hemorrhoid that most frequently causes symptoms is the acute thrombotic one. Internal hemorrhoids may vary from the simple, uncomplicated type, without symptoms and discovered on routine examination, to more severe types which may show slight ulceration with intermittent bleeding or prolapse, strangulation, and gangrene.

Infection may complicate the picture.

External Thrombotic Hemorrhoids.—This is a frequent type of hemorrhoid which is characterized by a painful swelling of acute onset, usually at the anal margin. The swelling has a pronounced bluish tint, and in its earlier stage is extremely tender to the touch. In size it may vary from that of a small shot to that of a walnut. When situated within the grasp of the anal sphincter, the smallest clot may cause intense pain. In the case of a large clot which is allowed to go untreated, pressure necrosis of the distended skin may result in ulceration, hemorrhage and sometimes infection. The only lesion that is likely to be confused with an external thrombosed hemorrhoid is a small marginal abscess. Observation for a day is usually sufficient to establish the differentiation.

The most effective *treatment* is excision of the clot and the ruptured vein. This is especially indicated when the patient is seen early with a tense, firm swelling. When the swelling is soft and has been present for several days, absorption of the clot has already begun and conservative treatment will often be sufficient. Rest, frequent application of hot compresses, and attention to bowel function will relieve the distress.

Excision of the hemorrhoid can be readily carried out in the office under local anesthesia. The limited area is surgically prepared, the hair cut away, and a skin antiseptic is applied.

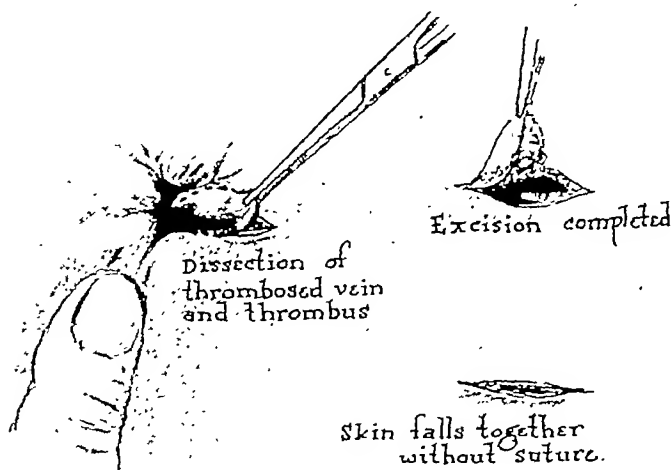


Fig. 111.—Excision of thrombosed hemorrhoid.

With a fine gauge needle the injection of procaine or other anesthetic solution is begun well beyond the outer limits of the swelling. The solution is then carried beneath the mass and along its outer margin so that the entire area is slightly elevated.

A wide elliptical incision is essential to permit complete dissection of all clots and to prevent prompt recurrence or complication (Fig. 111). After the entire overlying skin is cut away, the clots will either extrude readily or they can be cut away from their fibrous attachments. As a rule, bleeding is slight and firm pressure will control it. Occasionally, liga-

tion of the vein at the inner margin of the incision will be necessary. The wound margins need not be sutured.

It is essential that sufficient skin be removed to permit slight separation between the edges of the wound as the tissues retract and fall into place. Overlapping of skin margins allows secretions to accumulate, with possible infection, or permits the accumulation of slowly oozing blood with the formation of new clots. Vaseline gauze and a dressing firmly applied complete the procedure.

The patient should be allowed to rest about twenty-four hours, less if the wound is very small. Irrigation of the wound or hot compresses applied after defecation and several times daily will provide much comfort and adequate cleanliness of the area. The wound should be inspected and dressed at intervals of one or two days to insure that no infection occurs and that healing proceeds satisfactorily. Healing is complete in five to eight days, depending upon the size of the wound.

Internal Hemorrhoids.—A considerable proportion of internal hemorrhoids can be satisfactorily treated by conservative methods without surgical removal. In addition to those general medical measures which are important in controlling the causative factors, the most effective and most widely employed treatment among non-surgical measures is that of injection. Although treatment by injection has very definite limitations, it also has a wide field of usefulness and, in suitable cases, is an effective procedure. Its use will depend upon the extent of hemorrhoidal development and upon the degree of inflammatory change that may have occurred in the hemorrhoids.

Simple, uncomplicated internal hemorrhoids are the most suitable for treatment by injection. This will include internal hemorrhoids of moderate size which do not prolapse and which show no infection and no inflammatory changes, such as thrombosis. In this more or less limited group entirely satisfactory results, from the standpoint of symptomatic relief and permanent cure, can be obtained. There are, in addition, many advanced cases, in which operation is advisable but in which it is contraindicated because of the patient's general condition, where injections may be employed to provide a considerable degree of symptomatic relief.

Injection should never be employed in the case of external hemorrhoids or for internal hemorrhoids which are strangulated and thrombosed or which are associated with infection and ulceration of the rectum. In those internal hemorrhoids which prolapse frequently on slight provocation or which have become merely fibrous polypoid masses, the treatment is generally ineffectual.

Preliminary Preparation.—A few simple preparations are advisable before treatment is given. The patient should be instructed to empty the bowels beforehand and should plan his time so that he can rest for the remainder of the day after the injection has been given. During the period of treatment he should have a daily bowel movement accompanied with a minimum of effort. Purgatives are to be avoided, but mineral oil or a very mild laxative can be employed effectively. Enemas are not advisable for several days following the injection.

Injection Treatment.—A number of agents have been used for injection. Of these a 5 per cent solution of quinine and urea hydrochloride has been found the most generally satisfactory. Special syringes and needles are available, but any syringe may be employed which has an extension 3 to 4 inches long, to the end of which a small caliber needle can be attached.

A tubular anoscope, of the Martin type, should be used. It provides a complete view of the hemorrhoidal area and can be inserted and manipulated in the anal canal without discomfort to the patient. The patient can be satisfactorily placed on his side in the Sims or a similar position. Preliminary insertion of the finger facilitates passage of the anoscope, by slightly dilating the sphincter and by revealing slight variations in the direction of the anal canal.

With adequate light, the hemorrhoidal area is inspected and one hemorrhoid, usually the largest first, is selected for injection. It is brought into greater prominence by rotating the speculum until its bevel edge encompasses the mass. The site selected for injection should be near its inner margin, as far above the pectinate line as possible.

The area is cleansed with an aqueous antiseptic solution and the needle is inserted well beneath the mucosal surface,

but not necessarily into the body of the hemorrhoid. It is well to withdraw the plunger to make certain that the needle has not entered a vein. This, however, is not a frequent likelihood. The solution is injected slowly until there is uniform distention of the mass or until the surface of the mucosa begins to blanch. The point of the needle can be moved about slightly so that the solution can be better distributed. The amount to be injected will vary considerably, depending upon the size of the hemorrhoid, but it usually averages from 1 to 1.5 cc.

When sufficient solution has been injected, the needle is withdrawn and no further application is necessary. The injection of a single hemorrhoid should complete one treatment. The patient can immediately return home, but he should rest for the remainder of the day. Injections are repeated at intervals of five to seven days until all of the hemorrhoids are treated. If the location of the injections is noted on a chart, there is less likelihood of reinjecting a hemorrhoid in which the induration from a previous injection has not entirely subsided. Six to eight injections are usually sufficient.

The patient should be examined after an interval of a month or more following completion of the treatment. By this time all induration will have entirely subsided and, if any small areas of hemorrhoidal tissue remain that have not been sclerosed, these can be injected. During the period of treatment and afterwards, bowel function should be restored to as nearly a normal condition as possible. Defecation should be accompanied with little or no straining and any factors which tend to produce such effort should be corrected. Excessive physical efforts, such as lifting of heavy objects, are to be avoided.

When carried out carefully in suitable cases of hemorrhoids, injections provide an entirely effective means of treatment. Although of value in many other cases not considered entirely suitable, the method has definite limitations, of which the patient should be made aware. Frequently under such conditions, after irregular periods of treatment and relief, injections prove of decreasing value and ultimate operation becomes essential for cure.

Anal Fissure.—Anal fissure is a common lesion of the anal canal which causes a degree of discomfort entirely out of proportion to the actual pathologic process. Intense pain,

brought on by the passage of a stool and usually followed by a slight amount of bleeding, are the characteristic symptoms. As a rule, the presence of a fissure can be readily determined if the area is inspected while the buttocks and perianal margins are retracted, with the patient lying on his side and bearing down slightly. In more than 90 per cent of cases the fissure will be found situated in the mid-posterior wall of the canal at the mucocutaneous junction.

Digital or instrumental examination is made with difficulty because of marked sphincter spasm and aggravation of the pain on any attempt to pass by the muscle. Examination can be facilitated by the use of local anesthesia. A small cotton applicator saturated with a 10 per cent cocaine solution can be gently applied to the surface of the fissure for several minutes. This is usually sufficient to permit of more complete inspection.

Treatment of the fissure will depend largely upon the amount of local change present and, indirectly, upon its chronicity. Those fissures which have been present either continuously or intermittently for long periods will usually require radical excision. The chronic fissure will be found to have a deep, irregular base with thickened and fibrotic edges, and usually an hypertrophied tag of skin, the "sentinel pile," will be found at its distal end. In contrast, many acute fissures will satisfactorily respond to treatment by more conservative methods, provided that there are not also present other pathologic conditions which will require operation.

Injection Treatment.—In the fissure of recent development, the injection of an agent which provides anesthesia for several days and permits relaxation of the acutely spastic sphincter, will bring about a cure in a considerable number of such cases. For this purpose, a fresh solution of 1 per cent quinine and urea hydrochloride has been found effective and the agent least likely to produce complications.

After preliminary surface anesthesia and preparation of the skin distal to the lesion, the fissure is exposed to view as thoroughly as possible. A fine calibre needle (27 gauge) is employed with the ordinary hypodermic syringe. The needle is inserted into the skin just beyond the outer end of the fissure and is carried just beneath the base of the ulcer to its inner

end (Fig. 112). As the needle is withdrawn, a few minims of the solution are slowly injected until the entire base has been lightly infiltrated. From 0.5 to 1 cc. of solution are sufficient. Too much should not be employed, and it is important that no pooling be permitted to occur.

There is intense pain for a few seconds as the solution enters the tissues, and the patient should be warned to expect this. However, this pain passes very quickly and is followed by complete anesthesia of the painful area. No further applications are necessary. The patient should be instructed to secure a moderate degree of rest and to bring about a soft daily stool with the aid of a bland diet and a mild laxative. Anesthesia

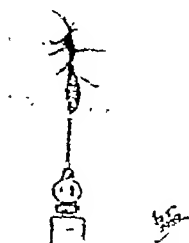


Fig. 112.—Injection of 1 per cent quinine and urea hydrochloride under base of acute fissure.

with 1 per cent quinine and urea hydrochloride solution will last from three to six days, sufficient to permit healing in many cases. If not, the injection can be repeated. When a second injection is not effective, it is not advisable to repeat it again and, as a rule, excision of the fissure will be necessary.

Simple divulsion of the anal canal under anesthesia is not sufficient to cure the chronic fissure and in the acute form will usually accomplish no more than the injection.

Anal Pruritus.—Anal pruritus may be the result of many etiologic factors and the variation in the symptoms may be so great that no single plan of treatment is applicable to all cases. Early in the disease, the itching occurs intermittently and may be slight or transitory. Later, it assumes a chronic,

intractable form with fairly characteristic skin changes in many cases. From the standpoint of etiology, most cases of anal pruritus are of the direct type, *i.e.*, due to some pathologic condition that may involve the anorectal area. Most common of these conditions are hemorrhoids, anal infections, or ulcerations. Included under this type also are skin infections, especially those due to fungi. Pinworms may be an occasional factor. The indirect type is relatively infrequent and includes the following: (1) anal pruritus of allergic origin, (2) that secondary to disease of the pelvic viscera and reflex in nature, and (3) neurogenic anal pruritus. As a rule, a diagnosis of pruritus of an indirect type is made only after every possible direct factor is excluded.

Treatment must include the eradication or control of any underlying cause, to the extent to which this is possible, in addition to such local measures as may improve the perianal skin and provide some immediate measure of relief. Correction of associated pathologic conditions is of particular importance if they are associated with some type of discharge, such as a fistula or a draining sinus. Discharging lesions are more frequently a causative factor in pruritus than such conditions as hypertrophied papillae or a fissure.

Not infrequently, a moderate development of hemorrhoids, especially if associated with some eversion of the mucosa, produces a persistent pruritus. In such cases, sclerosing injections into the hemorrhoid, which will also serve to take up the slack in the mucosa, will bring about a cure of the pruritus.

The treatment of the associated anorectal disease will be determined by the specific nature of the changes present and cannot be discussed in detail. In some instances study of the patient's problem must include a complete medical examination. While disease of the pelvic viscera or of more remote organs is not a frequent cause of anal pruritus, the latter condition will not be controlled as long as the underlying pathology persists.

The most important factor in prolonging the pruritus and in accentuating the changes in the perianal skin is the trauma that results from scratching. It increases the inflammatory changes, invites further infection of the deeper layers of the skin, intensifies the symptoms and prolongs the disease. Dur-

ing the period of investigation and of treatment of the associated anorectal pathology, many agents have been employed to aid in control of the scratching. Phenol is probably the most effective antipruritic agent and the basis of most preparations used for this purpose. It is often necessary to employ it in concentrations of 5 to 10 per cent, in either a thin oil or in a lotion. It can be advantageously combined with an anesthetic agent, either cocaine 1 to 2 per cent, or one of the newer synthetic preparations. A small pledget of cotton, lightly saturated with the liquid, can be applied and allowed to remain in place.

Fungus infections of the perianal skin are fairly common, although opinions differ widely as to their frequency. The characteristic skin changes are not always present and examination of scrapings is the only certain means of arriving at a diagnosis. The condition is not always associated with trichophytic disease elsewhere in the skin. Most of the fungicidal preparations which are in general use are irritating to the perianal tissues and must be employed in weaker concentrations. An effective and relatively non-irritating preparation is Castellani's paint. This is applied carefully with a camels'-hair brush, daily or every other day in and about the perianal folds, until the infection is controlled.

Injection of Alcohol.—In spite of the correction of possible underlying pathology and treatment of the perianal skin, an appreciable number of cases of anal pruritus will be found to persist and to be intractable to ordinary forms of treatment. For these obstinate cases more radical measures are necessary, and of such measures, the subcutaneous injection of alcohol has been found to be the most effective.

The patient is placed in the Sims position and the perianal area is surgically prepared. Only a segment of the perianal skin—one-fourth or one-fifth of the area—is selected for treatment at one time (Fig. 113). Just beyond the outer edge of the involved skin, a small wheal is raised by the injection of procaine hydrochloride. Through the wheal a needle of 22 gauge and about $2\frac{1}{2}$ inches long is passed under the skin and a 2 per cent solution of procaine hydrochloride is injected subcutaneously in as thin a layer as possible. Without withdrawal of the needle, and by passing it back and forth, the fan-shaped

segment of skin is infiltrated from the border of normal skin to the mucocutaneous margin. From 3 to 5 cc. of the anesthetic solution is required.

The needle is then carried to the medial or inner margin of the anesthetized area, a second syringe is attached, and 70 per cent ethyl alcohol is injected as the needle is withdrawn through the tissues. By moving the needle back and forth the alcohol can be so distributed as to distend the skin uniformly and without too much tension. The anal folds must be smoothed out as the alcohol is injected to permit even distribution and to prevent pooling. The amount of alcohol injected is slightly less than the amount of procaine solution,

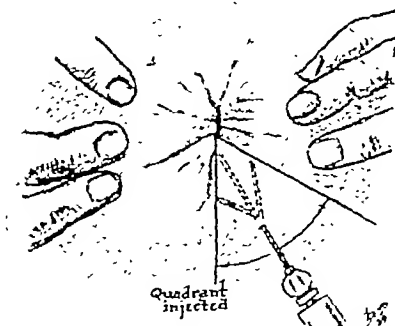


Fig. 113.—Subcutaneous injection of 70 per cent alcohol into one segment of perianal area after preliminary anesthesia with 2 per cent procaine hydrochloride.

and it must be injected within the limits of the anesthetized area.

Following the injection an antiseptic dressing is applied and the patient is allowed to return home. He is advised to carry out adequate cleansing of the area and to apply hot saline compresses three or four times daily for several days.

The same procedure is then repeated at intervals of a week or so until the entire perianal skin has been so treated. Depending upon the area injected at one time, from four to six treatments are necessary, requiring a total quantity of 15 to 20 cc. of alcohol.

Several *precautions* should be observed. The alcohol must

be placed in the loose subcutaneous tissue and not into the skin. The anal sphincters must not be injected and too large a quantity must not be placed into a small area or under tension. An occasional complication may be encountered in the form of a small slough. Starting as an abscess three or four days after injection, a portion of skin over the injected area may become necrotic and slough. Except for the discharge, no discomfort is usually experienced and healing takes place satisfactorily. No special measures are necessary other than those ordinarily employed in the treatment of a small open wound in this area.

Anal Cryptitis.—It is not uncommon to find patients who complain of annoying symptoms due to a mild inflammatory process involving the anal crypts and papillae. The complaint is that of a constant discomfort or burning sensation at the anus which is increased with defecation. Usually associated with the cryptitis is some degree of sphincter spasm which adds to the discomfort and interferes with normal bowel function.

The presence of cryptitis as the cause of these symptoms cannot always be determined with certainty, but examination will usually reveal suggestive evidence. Because of tenderness and muscle spasm, digital exploration must be carried out very gently. A localized point of tenderness will be found, sometimes with a noticeable thickening of the tissues. Enlarged papillae, often associated with the cryptitis, will be readily felt by the examining finger. Inspection of the canal, through the carefully inserted anoscope, will reveal an area of redness and edema surrounding the crypt as well as the elongated, whitish papilla which will be very tender to touch. Inflammation of the papillae is usually not found alone but as an extension from the anal crypts. An increase in the depth of the crypt, determined by inserting a hooked probe into it, is not an indication in itself of pathologic change.

Treatment.—In most cases, conservative medical measures will provide relief. The anal canal and terminal rectum should be irrigated after each bowel movement with warm saline or witch hazel water. This can be carried out with a small catheter passed back and forth in the canal as the patient sits over the toilet, or as a small enema of 6 or 8 ounces. A hot sitz bath, following, will afford comfort and considerable relaxa-

tion of the spastic muscles. At bedtime, and if necessary during the day, a retention enema is given of 2 ounces of warm olive oil in which is mixed a powder such as benzocaine (gr. v) and bismuth subcarbonate (3ii). When the inflammatory changes are more marked, 5 to 10 grains of iodoform can be added for its beneficial effect upon the anorectal tissues. The patient is advised to rest, given sedatives as needed, and instructed to follow a bland diet and secure a daily soft stool. Various soothing ointments or suppositories may be employed, but they should be applied only after the area is cleansed of irritating fecal matter.

These measures will usually be sufficient unless the cryptitis is associated with other pathologic conditions of the anus or rectum. When such are present, appropriate treatment for them will be necessary before the inflammatory process in the crypts will be controlled. Occasionally when the inflammation has persisted for a prolonged period and fibrosis about the crypt has resulted, its *excision* is necessary. This can be carried out under local anesthesia without hospitalization. The involved crypt and papilla is exposed by means of a bivalve speculum and its base, together with the skin distal to it, is infiltrated with the anesthetic solution. A hook-shaped probe is then inserted into the crypt and carried outward under the skin of the anal margin. The skin and mucosa which overlies the probe is then cut away with scissors leaving a narrow V-shaped wound. At times, a bleeding vessel is found at the inner end of the wound which will require a ligature.

The postoperative treatment for four or five days will consist of simple cleansing of the area and the application of a mild antiseptic dressing. The measures employed in the usual management of cryptitis will provide much comfort and aid in healing.

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INTRA-OCULAR OPTIC NEURITIS: ITS ETIOLOGY, DIAGNOSIS AND TREATMENT

THE subject of this discussion is intra-ocular optic neuritis (usually spoken of as "optic neuritis"), and we will begin by presenting a brief case history which will serve to bring out the symptoms, signs and chief points of interest in this very serious disease:

Case History.—Mr. A. B., forty-three years of age, complains of dimness of vision in each eye. He states that he first became aware of this blurring about two months ago, that it is more marked in the left eye than in the right, and that it gradually has become worse. He has no pain in his eyes, no headache, and complains of no symptoms other than the blurred vision. On examination we find the vision in his right eye reduced to 6/30, and in the left eye to 6/60. The right pupil is 3 mm. in diameter, the left 4 mm.; both react somewhat sluggishly to light, but normally to convergence. The palpebral conjunctivae are hyperemic, but other external conditions are normal. There are no evidences in the cornea of either eye of previous disease or injury. The irides are of good color; the pupillary margins are free and show no synechiae. The muscle balance, ocular rotations and tension are normal.

Ophthalmoscopic examination shows, in the right eye, media clear; the optic disc is much redder than normal, its margins are obscured, and upon its surface is a very faint grayish striation which extends a short distance into the retina. The arteries are normal in course and caliber, the veins full and slightly tortuous. The left eye shows the same condition, slightly more marked. The form fields show an irregular concentric contraction, not very marked, and there is enlargement of the blind spot. Diagnosis, optic neuritis.

Now, the points to be noted in an analysis of this history; which is quite characteristic of optic neuritis, are that the disease was insidious in its onset, that it is bilateral, and that the only symptom of which the patient complained was the blurred vision. Also that the pupil of the eye more markedly involved is larger than that of the other eye, the marked reduction in the acuity of vision, the characteristic eyeground picture and the enlargement of the blind spot.

Optic neuritis is not a disease in itself but is to be regarded as a manifestation of a serious disorder elsewhere in

the body, and so our obvious duty is to discover, if possible, the underlying disease which has caused it in order intelligently to prescribe treatment for the relief of this condition.

Anatomy of the Optic Nerve.—Before proceeding with a systematic investigation into the etiology of optic neuritis, it is essential for us briefly to review the gross anatomy of the nerve, especially that portion which is seen with the ophthalmoscope:

The optic nerve is about 50 mm. or 2 inches in length, and extends from the optic chiasm to the retina, passing through the optic foramen, the orbit, and the sclera. It thus has an intra-cranial portion, an orbital portion, and an intra-ocular portion. In its orbital portion it is shaped somewhat like the letter S to permit free movement of the globe. It is considered by some observers to be a projection forward of a portion of the white substance of the brain; like the brain, it is surrounded by three membranes, the dural, arachnoidal and pial sheaths. The space between the dural and pial sheaths is known as the "intervaginal space," and this space is divided by the arachnoidal membrane into a subdural space and a sub-arachnoidal space, both communicating with the corresponding cerebral spaces. At the sclera it terminates in a cul-de-sac, the sheaths of the nerve blending into the tissue of the sclera. The nerve is about 3 mm. in diameter in its orbital portion, while at its entrance into the eyeball it is much thinner, being at this point only 1.5 mm. in thickness.

The optic nerve consists of nerve fibers and loose connective tissue, the fibers having a medullary sheath but no sheath of Schwann. From the pial sheath extend inward connective tissue septa, which serve to divide the nerve fibers into numerous separate bundles. Between these are to be found lymph spaces; vessels from the pial sheath supply the nerve in its orbital portion. The central artery enters the nerve about 15 mm. behind the eyeball, while the central vein leaves the nerve slightly nearer the globe and somewhat lower than the artery.

At the point where the nerve pierces the sclera to enter the eyeball, fibers from the inner layer of the sclera stretch across the foramen, and these fibers, together with others from the modified choroid, combine to form a sieve-like arrangement

known as the "lamina cribrosa," through the openings of which pass the separate fiber bundles of the optic nerve. Here is formed what is known as the "head of the optic nerve," the "optic disc," or the "papilla." These names are used interchangeably. The name "papilla," although widely used in this connection, is somewhat of a misnomer as it implies an elevation of the optic nerve at its entrance into the eyeball, whereas the normal nerve head rarely if ever is higher than the retina about it. The fibers of the optic nerve here lose their medullary sheath, bend outward, and are distributed in the nerve fiber layer of the retina.

The Normal Optic Disc.—Although the ophthalmoscopic picture of the normal papilla is familiar to most of us, it might be well briefly to review it at this point. In order properly to study the disc we must proceed in a systematic manner and carefully note its form and size, color, margins, level and vessels. The form of the normal nerve head is, as a rule, round or sometimes slightly oval, its color is pinkish or yellowish-red, usually more pronounced over the nasal half, the temporal portion being somewhat paler, contrasting strongly with the reddish color of the rest of the fundus. The margins are sharply defined, usually more so at the outer side, where two rings often may be observed, an inner or scleral ring, light in color, and an outer or choroidal ring of a darker color. At the center of the disc is seen a shallow depression or excavation, produced by the separation of the nerve fibers and known as the "physiological cup." The level of the disc is the same as that of the retina surrounding it. The vessels are the central artery and vein. They appear near the center of the disc and usually divide, forming superior and inferior branches; these again divide into nasal and temporal branches. The arteries are smaller in caliber than the veins, brighter red in color and pursue a straighter course. Along the center they show a bright reflex. The veins are thicker, darker and more tortuous than the arteries, and the light streak less pronounced. Both vessels, as a rule, follow the same course.

Thorough familiarity with this normal picture is quite essential for an intelligent interpretation of the pathologic nerve head.

The Pathologic Disc.—The pathologic changes which

occur in the optic disc or papilla and which are of special interest to us in this discussion are hyperemia, optic neuritis (also called "papillitis") (Leber), and choked disc. In order to arrive at a correct diagnosis of optic neuritis, it is quite necessary to differentiate sharply between these various conditions, as the diagnosis depends largely, although not entirely, upon the ophthalmoscopic picture. Retrobulbar neuritis must be considered briefly, and pseudoneuritis, an anomalous but not pathologic condition, must also be mentioned.

Hyperemia of the Disc.—Hyperemia of the papilla alone, without any other symptoms, must be carefully considered, as the color of the disc has rather wide limits of physiologic variation. A papilla always is a brighter red in a person of light complexion than in a brunette, and it also appears redder in young people than in older persons. Prolonged strain of the accommodation in far-sighted persons and presbyopes may produce hyperemia of the disc. In this condition the capillaries and small vessels, which normally are not seen, become visible and cause an abnormal reddening of the disc, thus reducing the normal contrast between the papilla and the retina. Although this is not a true inflammation and there is no exudate present, the nasal margins of the disc may be blurred, due to the presence of a small amount of serum between the nerve fibers in this area.

Hyperemia of the papilla also may appear as a symptom of a pathologic process elsewhere in the eye, and may be noted in such diseases as iritis or irido-cyclitis, or in injuries of the globe, although there is no disease in the nerve itself. Careful consideration must be given these causes before a hyperemia of the disc rightfully can be regarded an early stage of optic neuritis or choked disc.

Pseudoneuritis.—A change from the normal appearance of the papilla that is likely to lead to mistakes in diagnosis is that condition, not infrequently seen, which is known as "pseudoneuritis." Here we see the color of the disc distinctly redder than normal, with marked blurring of the margins. There may be some prominence of the nerve head with dilatation and slight tortuosity of the vessels. This is regarded as a congenital condition and has no pathologic significance. It not uncommonly is observed in patients with hyperopia or hyper-

opic astigmatism and, as lowered visual acuity sometimes is accompanied by these errors of refraction, another symptom of true optic neuritis, impairment of vision, is present. As a rule, however, the vision is normal, or can be brought to normal by a careful correction of the refractive error.

It is not always easy to differentiate this condition from true optic neuritis, especially when the case is first seen, and it may be necessary to keep the patient under observation for a certain time in order to determine definitely whether or not the condition is remaining stationary. However, because of the absence of visual defects, abnormalities of the field, or enlargement of the blind spot, it can be differentiated definitely from optic neuritis, and also by the absence of edema about the papilla, which is seen in most cases of optic neuritis and which never is present in pseudoneuritis. The fact that the condition shows no tendency to become worse from time to time, but rather remains stationary with no loss of vision, is an important point in the differential diagnosis.

Optic Neuritis.—Now, keeping in mind the picture of a normal papilla, and its appearance when modified by hyperemia or pseudoneuritis, let us examine the eyeground of a patient with true optic neuritis. Here we see a different picture: The color of the disc is altered, being a reddish or grayish red. It is often radially striate, and its outlines are invisible due to a cloudiness caused by the exudate, which frequently extends over its margins to the adjoining retina. As a result of this, the papilla appears much larger than normal, and may become so obscured because of the infiltrate that its position can only be determined by noting the point where the central vessels emerge from the disc. The arteries appear either normal or slightly contracted, and may be hidden in spots by the exudate. The veins are dilated and somewhat tortuous owing to the pressure being placed upon them by the swollen nerve. Small hemorrhages may be seen on the disc or in the area about it. It is important to notice the surface of the nerve head, as this being swollen, is somewhat elevated above the surrounding retina. When the infiltration markedly involves the retina about the nerve, the condition is known as "neuroretinitis."

Choked Disc.—In any discussion of optic neuritis, we must, of necessity, consider that very important lesion of the

nerve head known as "papilledema" or "choked disc." Although the ophthalmoscopic appearances of these two conditions are frequently quite similar, it is necessary to make a definite distinction between them, chiefly because of the factors concerned in their production. In optic neuritis we are dealing with a true inflammation which has the same symptoms that characterize inflammation in any other part of the body, namely, congestion and exudation; whereas choked disc is produced, for the most part, by mechanical compression of the central vessels of the nerve. In papilledema, the disc is greatly swollen and appears enlarged by the edema. It is gray or grayish-red and sometimes may present a translucent appearance. The margins may be fairly well defined, and the surrounding retina may not show any marked disturbance, although delicate radial striations may be present, somewhat obscuring the margins. The surface of the disc is markedly elevated, projecting forward into the vitreous somewhat in the shape of a mushroom. The arteries are contracted, but the veins are greatly dilated and tortuous, and hemorrhages are sometimes seen in the retina. A grayish striation corresponding to the swollen nerve fibers may be seen upon the papilla.

The differences between optic neuritis and choked disc have to do mostly with the degree of swelling of the nerve and the spreading of the inflammatory process to the retina surrounding it. In the absence of signs of inflammation in the disc, and the very evident projection of the engorged nerve head into the vitreous, we are justified in distinguishing between the two conditions. The amount of swelling of the disc can be roughly estimated by the manner in which the vessels bend as they leave the elevated surface of the disc to pass over into the retina; also by measuring with an ophthalmoscope the difference in refraction between the most elevated portion of the engorged nerve head and the retina. In optic neuritis, the swelling of the disc is only moderate, there is no marked bending of the vessels at the disc margins, and only slight, if any, elevation. However, even giving due consideration to these points of difference, optic neuritis and choked disc are frequently so similar in appearance that it is often quite difficult to distinguish between them.

Retrobulbar Neuritis.—In addition to the optic neuritis

which is located at the intra-ocular end of the nerve, an inflammation occurs in the orbital portion of the nerve which is known as "axial" or "retrobulbar neuritis." In this form of the disease the ophthalmoscopic appearances are at first negative and may remain so. Later, however, if the inflammation is severe, the disc margins may become blurred and the disc may show some hyperemia of its surface with slight fulness of the veins. This is rare, and in the great majority of cases the papilla shows no pathologic changes. The symptoms are blurring of vision, beginning at the center of the field and frequently rapidly progressing to almost complete blindness. A central scotoma usually is present, and is the most important point in the diagnosis in the absence of any pathology involving the disc.

Optic Atrophy.—It must be remembered in connection with optic neuritis, and this is very important, that a certain degree of atrophy of the optic nerve almost always follows papillitis, the extent of which depends on the severity of the inflammation and the duration of the disease. The term "neuritic atrophy" is applied to this condition. This is characterized mainly by pallor of the optic disc and contraction of the arteries, and is always accompanied by a marked reduction in the visual acuity; hence the necessity of an immediate investigation into the cause of the disease and the early institution of remedial measures.

Now, to repeat, papillitis is not a disease in itself but is an indication of disease elsewhere in the body, the infection being brought to the nerve by the intracranial fluid, lymph or blood stream, or being transmitted to it from a lesion in the orbit or a nearby structure. Let us proceed, therefore, to consider some of the most important factors in the etiology of the disease.

Etiology of Optic Neuritis.—*Disease of the brain* may produce optic neuritis, meningitis in its acute and chronic forms being a frequent cause, and if we remember that the optic nerve and its membranes are a direct projection forward of the brain and its membranes, it easily can be understood that an inflammation in the latter structures readily can be extended downward to the nerve and its sheaths and so produce an inflammation which is usually designated as "descending

neuritis." This type of papillitis can readily be caused by meningitis; other causes arising in the brain are hemorrhage, cerebral softening, hydrocephalus, abscesses, sinus thrombosis, aneurysm, or lesions of the pituitary body.

Meningitis, however, is the most frequent cause, especially the tubercular type. In tuberculosis, primary infection of the nerve seldom occurs, and when the nerve is involved, the inflammation is usually due to a diffuse descending neuritis resulting from tuberculous meningitis. It is impossible to recognize this type of papillitis from the ophthalmoscopic picture alone unless tubercles are seen on the disc or in the choroid, in which case the presence of this particular infection may be indicated. It is seen most frequently in young people or children, and is regarded by some observers as the most frequent ocular symptom of tuberculous meningitis.

Optic neuritis may also arise in association with a *deformity of the skull*, notably oxycephalus, also known as "peaked" or "tower" skull. Atrophy of the nerve usually follows.

Optic neuritis is occasionally observed in the course of many of the acute *infectious diseases*, and among these may be mentioned scarlet fever, smallpox, measles, pneumonia, diphtheria, typhoid fever, mumps, and erysipelas. In the opinion of one observer (Uhthoff), the nerve disturbance arises more often during convalescence, and in all probability is the result of the toxins circulating in the blood and is not due directly to the microorganism. We must also mention in this connection *epidemic cerebrospinal meningitis*. In this condition the entire optic tract is involved as a result of the meningococcus being carried downward by the cerebrospinal fluid.

Of the chronic infections, the most common are *syphilis* and *tuberculosis*, and of these two, syphilis is the more frequent cause. Both nerves are usually involved in syphilitic neuritis. The infection begins primarily in the vessels of the pial system or the central vessels, producing first vascular changes and, later, interstitial neuritis, resulting in a local or diffuse inflammation of the papilla. This type of neuritis usually can be recognized by the great edema and infiltration around the disc and the presence of a diffuse central opacity of the vitreous, which serves still further to obscure the ophthalmoscopic picture. In syphilis, primary inflammation of

the nerve is the rule, and extension downward from the meninges is rare, although it is entirely possible for a syphilitic basilar meningitis to pass from the meninges to the optic nerve and produce the picture of a descending optic neuritis. In these cases, however, we would probably see other symptoms referable to the eye muscles, such as paresis accompanied by diplopia, and accommodation and pupillary changes. Hereditary syphilis rarely produces optic neuritis, and when it does, it is usually associated with meningitis.

Inflammation of the optic nerve may occur in the course of *renal disease* and *diabetes*. In the so-called albuminuric retinitis, the papilla and retina immediately surrounding it are frequently intensely hyperemic, and the nerve head may be so greatly swollen as to be indistinguishable from choked disc as seen in tumor of the brain. The presence of white spots in the retina with scattered hemorrhages and the frequent presence of the star-shaped figure at the macula are quite suggestive of a renal origin of the disease. In diabetes, the papilla is frequently very red and slightly hazy, and white spots and hemorrhages are often seen in the retina. In these cases the retina is so much more affected than the nerve that the neuritis would seem to be of secondary importance.

Papillitis also may be caused by *disease in the orbital region, tumors, abscesses, periostitis, or cellulitis*, especially when located in the region around the optic foramen. Suppurative infections within the *accessory sinuses* also may involve the optic nerve in an inflammatory process, especially those originating in the posterior ethmoidal cells or sphenoidal or frontal sinuses. Unless the orbits or sinuses of both sides are involved, the neuritis is unilateral. Occasionally papillitis of this form will resemble retrobulbar neuritis or even choked disc. It is important to examine the sinuses and their drainage in cases of doubtful origin.

Purulent *disease of the middle ear or mastoiditis* giving rise to intracranial complications may produce papillitis, the nerve being only mildly affected at first. Should meningitis, brain abscess, or sinus thrombosis develop, however, the redness and especially the edema of the nerve increases rapidly. Under these circumstances immediate operative interference is indicated.

Among *other causes* of optic neuritis may be mentioned such toxic agents as lead, atoxyl and methyl alcohol. It also is caused by anemia, chlorosis, menstrual disturbances, pregnancy and lactation, myxedema, arteriosclerosis and exposure to cold. Occasionally it is seen after arsphenamine injections.

Pathology.—In considering the pathology of the inflamed optic nerve, we must remember that the nerve is enveloped by a prolongation of the sheaths of the brain, and therefore an inflammation of the meninges readily is transmitted to the nerve sheaths, producing what is termed “descending neuritis.” We also must bear in mind that the connective tissue septa, freely supplied with blood vessels between the bundles of nerve fibers, may receive infection carried by the blood and give rise to an inflammatory process starting around the vessels and extending to the septa, thus producing an “interstitial neuritis.” The nerve fibers are not involved in the process at first except by some compression due to the exudates and edema. Subsequently these exudates organize, producing a thickening of the septa, which is followed by degeneration and pressure atrophy of the nerve fibers.

Diagnosis.—The diagnosis of optic neuritis largely depends upon the ophthalmoscopic appearance of the inflamed disc, although not alone, and the importance of a careful differentiation from other lesions of the nerve head cannot be overestimated. A general systemic examination should be made early in every case, and should include a Wassermann test and urinalysis. If the neuritis is observed in one eye only, the sinuses on the same side should be examined at once, and an x-ray photograph made of these cavities. The teeth, tonsils and other organs also should be investigated. When bilateral, in addition to the examinations just mentioned, all the systemic causes previously discussed must be carefully considered.

Course.—Concerning the course of the disease, if the onset is acute, the symptoms may develop rapidly; usually, however, it runs a chronic course, the symptoms developing slowly and gradually becoming more marked. It often takes a long time for the inflammation to subside, and as it does so, the margins of the papilla again become visible and the retinal vessels and those on the surface of the disc appear contracted. The color is now altered, and the disc appears pale and begins

to show the signs of neuritic atrophy. The degree of these atrophic changes depends upon the intensity of the preceding neuritis; if the inflammation has been mild, the resulting pallor of the disc is not intense and some degree of vision remains, although if the nerve has been subjected to a severe inflammatory process, the atrophy is more marked, and the disc may become almost paper white, the vision being greatly impaired or lost completely.

Prognosis.—The prognosis is serious in all cases. It largely depends upon the duration of the inflammation and the disease producing it. If the cause can be determined and removed quickly, the outlook for the restoration of useful vision is favorable, otherwise considerable vision is sure to be lost. Should the disease remain untreated, great loss of vision or blindness may result.

Treatment.—In the treatment of optic neuritis, all measures must be directed toward the removal of the cause of the disease. Infections of the accessory sinuses, middle ear, or mastoid must receive appropriate treatment. If investigation points to syphilis as a cause, the prompt and vigorous use of mercury and the iodide of potassium often will produce rapid improvement. Neoarsphenamine also is used for this purpose instead of the older mercurial treatment. Sweat baths are also very efficacious. Even in nonspecific cases, the use of mercurial inunctions and iodides may be of great value. Measures to reduce inflammation also may be tried, and for this purpose the injection of a foreign protein has been recommended, usually in the form of milk or typhoid-paratyphoid vaccine, the patient being kept under close observation. All sources of local infection should be removed and the eyes put at rest; dark glasses should be worn. Abstraction of blood from the mastoid region may be tried. In cases where no apparent cause can be found, sweat baths and saline cathartics have been recommended.

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THE TREATMENT OF ACUTE AND CHRONIC KIDNEY DISEASE

THREE forms of kidney disease are generally included under the term "nephritis": (1) glomerulonephritis, or glomerular nephritis, an inflammatory and hemorrhagic disease of the kidney characterized pathologically by a diffuse glomerulitis; (2) nephrosis, marked primarily by degeneration of tubular epithelium; and (3) nephrosclerosis, or arteriosclerotic disease of the kidney, the result of primary vascular disease affecting the small arteries of the kidney, which follows essential hypertension. All can be grouped under the old fashioned term "Bright's disease" but only the first should properly be called "nephritis." Aschoff suggested that a more precise way of designating this widely different group of lesions would be "disorders of the kidney characterized by symptoms of Bright's disease."

While we are concerned with this whole group of disorders, we must restrict ourselves largely to a discussion of the treatment of glomerulonephritis.

ACUTE GLOMERULONEPHRITIS

Ten years after the first presentation of his work on kidney disease, Bright remarked: "It is a humiliating confession that although much attention has been directed to this disease for nearly ten years, little or nothing has been done toward devising a method of permanent relief when the disease has been confirmed, and no fixed plan laid down as affording a tolerable certainty of cure in the more recent cases." After more than a hundred years we still must confess to the first

difficulty, although we feel a little more secure in regard to the second.

The great majority of patients, perhaps 75-85 per cent of children and probably more than 60 per cent of adults, who suffer from a first attack of glomerulonephritis, will get perfectly well with very simple management, of which rest in bed is the most essential part. This rest must be continued until long after most of the acute symptoms of the disease have subsided or until it is clear that the process has become chronic and no more is to be accomplished by rest. This will be four to six weeks in the usual mild case of glomerulonephritis. Frequently, in such cases, the acute symptoms subside very rapidly (edema, hypertension, gross hematuria) and only slight albuminuria and perhaps a few red blood cells remain. This is especially true of children with acute glomerulonephritis, and keeping such children in bed becomes a difficult problem.

The next question that frequently arises is when to remove the tonsils, in cases in which the attack follows acute tonsillitis. This should be delayed until well after all the acute symptoms have subsided, probably at the end of six to eight weeks and even then one must be prepared, and advise the family that a slight exacerbation of symptoms may occur.

Sometimes cases that begin in the stormiest fashion do well and mild cases become chronic. Frequently it is most difficult to tell whether the case is becoming chronic; continued hypertension, pallor, hematuria and albuminuria, together with increased sedimentation time, gradual diminution in concentrating ability as measured by specific gravity tests, and reduction in the urea clearance figures will, of course, indicate progression. But, occasionally, a cure results even after symptoms have continued for many months and the reverse is unfortunately also true; that is, after apparent recovery progression into chronic disease still occurs. If complete recovery has not occurred at the end of a year, the case will almost certainly remain chronic and this, of course, is a disastrous result to be prevented, if possible, at all cost. In this regard, it is especially important to recognize the mildest cases in order not to neglect their care. There must be many very mild cases that escape attention exactly similar to the mild rheumatic disease that escapes attention but which later results in mitral stenosis.

In fact, it has been demonstrated that routine urinalysis two to three weeks after an attack of tonsillitis will permit detection of certain instances of acute glomerulonephritis that ordinarily would be missed.

It has been stated that rest in bed is the all-important factor in treating acute glomerulonephritis. Diet, contrary to general belief, is not especially important and if dealt with exactly as in dealing with any other acute infectious disease will be satisfactory. One does not need a measuring scale or an expert dietitian in dealing with diet in acute nephritis or, for that matter, in any stage of the disease. In the usual case small amounts of fruit juices are permitted for the first few days; then cereals, junket and custard are added; later, creamed vegetables, rice, butter, stewed fruit, in addition to milk and egg; and finally, a full dietary including meat.

This brings us to a consideration of the great bogey in kidney disease: the question of the protein in the diet. So much advance has recently been made in this respect that it will no longer be considered heretical to say that, in general, one restricts protein in glomerulonephritis at two periods only: at the beginning and at the end of the disease; at the beginning only because one is dealing with an acute infection in which heavy foods like meat would ordinarily be withheld, and at the end when renal failure occurs and the badly damaged kidney is having great difficulty in excreting not only the end products of protein metabolism but all other waste substances as well. We will encounter this problem again shortly.

It is a mistake to try to "flush out" the kidney in acute nephritis. On the contrary, at the very onset, fluid (and salt which, in the body, is inseparable from fluid) had best be restricted. About 800-1000 cc. of fluid in twenty-four hours in the beginning, and after a few days increased as determined by the urinary output, is a good general plan. Volhard subjects severe cases to the "hunger and thirst" treatment: no food or fluid for three to five days. I have not found such strenuous measures necessary. Fluid restriction is indicated more on account of the brain and heart than on account of the kidney. Cerebral manifestations (hypertensive encephalopathy) and heart failure are more to be feared than kidney failure in acute nephritis.

When hypertensive encephalopathy occurs or threatens (severe headache, nausea and vomiting, amaurosis, convulsions and coma), dehydration measures are to be instituted immediately. Magnesium sulfate daily by mouth is a good prophylactic measure and, if cerebral symptoms occur, it may be given intravenously (100–300 cc. of 2 per cent solution), or intramuscularly (4–10 cc. of 25 per cent solution or 2–6 cc. of 50 per cent solution), by mouth and by rectum (1–2 oz. of 50 per cent solution) every four hours until the blood pressure falls and remains at a low level. Venesection (200–400 cc.) and lumbar puncture are emergency measures to be employed for the attack. Lumbar puncture must be performed cautiously to prevent compression of the medulla into the foramen magnum.

Magnesium sulfate and fluid limitation are also helpful in heart failure in addition to the usual measures of rest, digitalis and morphine. Diuretics are contraindicated in acute nephritis. The mild ones are useless and potent ones (mercurials) are dangerous. There is no harm in trying glucose injections intravenously for anuria. *x*-Ray and diathermy over the kidney have not been helpful in my experience.

Sweating is an age-old institution in the treatment of acute nephritis but is losing favor. Sweat and urine are similar in content qualitatively, but the urine contains five to nine times more organic matter. Hence sweating, even in large quantities, can hardly assist the kidney in ridding the body of much waste material. Keeping the patient warm is sufficient; it is important to avoid chilling.

SUBACUTE GLOMERULONEPHRITIS

No special treatment is indicated for the edema of acute nephritis, which is thought to be due to increased capillary permeability. It is one of the first symptoms to subside as the patient recovers. If recovery does not occur and the patient passes into the subacute stage, edema may become one of the most perplexing and important problems in the management of the patient. It is well to remember that considerable fluid may be retained before pitting occurs. The regular use of the scales will discover such edematous tendencies. Always

look in the sacral region for edema if the patient has been confined to bed.

On the other hand edema may be very pronounced, accumulating in serous sacs as well as in the tissues. This variety of edema, associated with the nephrotic or hydremic syndrome—the clinical picture may exactly duplicate that of genuine nephrosis—is largely due to the continued loss of large amounts of albumin in the urine with depletion of blood proteins. It has been found that albuminuria must amount to at least 1 Gm. per day for hypoproteinemia to develop. When the level of blood proteins reaches 5 per cent, the question of salt becomes an important secondary factor in edema formation. The nephrotic syndrome interferes with nutrition, lowers vitality and predisposes to infection, and hence it is important to combat it if possible.

The principles of treatment may be outlined as follows:

1. Keep up nutrition with an adequate caloric intake.
2. Restore the colloidal osmotic pressure of the blood serum with an adequate protein intake, blood transfusions and possibly by injections of acacia.
3. Promote excretion:
 - (a) Through the kidneys, by means of diuretics (?).
 - (b) Through other channels, such as skin and bowel, by sweating and purgation (?), and by aspiration of effusion.
4. Restrict the intake of edema-producing substances such as sodium chloride.

With the low protein-salt poor diet usually employed in the nephrotic syndrome of kidney disease nutrition suffers. Severe degrees of wasting are often masked by the edema. The anemia-producing diet adds to the anemia of nephritis already present. It is not only important to give proteins, but the diet must be adequate in other respects: sufficient calories, minerals and vitamins. In a case which appears to be nephrosis it is much better to try a high protein diet in an effort to control the edema than to take a chance on a nephritic exacerbation by giving a mercurial diuretic to get rid of the edema.

Epstein deserves credit for calling an about-face on the

protein question. He employed high protein diets in cases of genuine nephrosis—two or three times the quantity of protein ordinarily ingested. As we began to understand that the fundamental mechanism of edema formation was the same in the nephrotic syndrome of glomerulonephritis, we began to use proteins in large amounts in such cases, and finally, a few courageous physicians dared to use a higher protein intake in other varieties of kidney disease, often with remarkable results. Thus Aldrich became discouraged with the prevailing treatment—low protein diet and removal of foci of infection—in chronic nephritis of childhood. In 1930 he changed his methods radically. Meat or eggs were ordered three times a day, salt was allowed to all those who were not definitely edematous, and vitamins were included in the diet. All of the patients began to look better. Clinical improvement in general health was noted within a few weeks. The death rate was decidedly reduced. Three cases showed complete disappearance of clinical evidence of the disease. The high protein diet did not cause elevation of blood pressure or increase of non-protein nitrogen. McCann and his associates have used similar measures in adults with chronic nephritis.

Since these pioneer observations, the taboo on protein is rapidly disappearing as far as medical men are concerned. It is no longer believed that protein is hard on the kidney, either normal or diseased. Various observers have produced kidney changes in rats by feeding large amounts of protein. It is questionable if the results can be applied to man. Efforts to reduce the blood nonprotein nitrogen by a low protein diet may be successful but effect a "laboratory cure" only. It is something like producing a drop in blood pressure in essential hypertension by means of nitrites or attempting to lower fever in infectious diseases by antipyretics. It is a question of treating a symptom instead of the patient, and it may do more harm than good. More will be said of this later. The laity are still convinced that meat is dangerous in kidney disease and high blood pressure and it may be almost impossible to convince them that their viewpoint is incorrect.

It has been generally accepted that a healthy individual ordinarily takes from 50 to 75 Gm. of protein daily. Ashe and Mosenthal, however, discovered that 60 per cent of 1000 peo-

ple studied in the course of a general physical examination ate 42 Gm. or less of protein daily. An adequate protein diet is made up of a generous helping of meat, fish or fowl, two eggs, one pint of milk and such other smaller amounts of protein as occur in cheese, milk, vegetables (legumes) and bread. Meat and egg white can be increased for a higher protein value and Page recommends edible casein, 20-30 Gm. in a glass of milk. Thus 100-125 Gm. can easily be given and balanced by sufficient carbohydrates. The question of the differences in the protein of animal and vegetable origin is not important from the standpoint of the kidney, but protein of animal origin is superior for purposes of nutrition. I have found O'Hare's simple method for determining the quantity of protein in the diet very useful and, although it has appeared in many books dealing with dietetics, it may be helpful to reproduce it here:

Nephritic Diet List of O'Hare.*—Any combination of the foods listed below may be selected. Foods not listed below must not be taken.

In Groups 1 and 2 there is a restriction in the total amount.

The foods in these groups must be served in full or half portions.

A full portion in Group 1 counts 1.

A full portion in Group 2 counts 2.

In Group 3 the quantity of each is not restricted, although you are urged to use discretion.

Your total score for the day should be Do not add salt or spices to the food after it has been cooked.

Group I

(Each Full Portion Counts 1)

<i>Full Portion</i>		<i>Vegetables, etc.</i>	<i>Full Portion</i>
Bread (white)	1 av. slice	Baked beans	1 tbsp.
Bread (graham)	1 av. slice	Lima beans	1½ tbsp.
Unceda biscuit	5 crackers	Potato, creamed	1 tbsp.
Shredded wheat	1 biscuit	Potato, mashed	1½ tbsp.
Graham crackers	5 crackers	Potato, baked	1½ tbsp.
<i>Cereals, etc.</i>		Potato, boiled	1½ tbsp.
Oatmeal	2 tbsp.	Canned corn	2½ tbsp.
Boiled rice	3 tbsp.	Green peas	2 tbsp.
Cornmeal mush	4 tbsp.	Beets	5 tbsp.
Cream of wheat	6 tbsp.	Spinach	4 tbsp.
Farina	6 tbsp.	Bananas	2 large
Macaroni	4½ tbsp.	Cream, heavy	¾ cup

*O'Hare, J. P. and Vickers, M. C.: Home Management of the Diet in Nephritis. J.A.M.A. 81: 1626, 1923.

Group II

(Each Full Portion Counts 2)

<i>Full Portion</i>		<i>Fish</i>		<i>Full Portion</i>
Milk1 glass	Cod, boiled1"x1"x1½"	
Egg1 egg	Haddock, boiled1"x1"x1½"	
Eggs scrambled1½ tbsp.	Halibut, boiled1"x1"x1½"	
Flour, sifted¾ cup	Mackerel, boiled1"x1"x1½"	
		Salmon, boiled1"x1"x1½"	
		Smelt½"x1"x1"	
		Oysters7 oysters	
		Crabmeat, canned2 tbsp.	
		Salmon, canned1½ tbsp.	
		Shrimp, canned6 small	
<i>Meats</i>				
Lamb chop, broiled¾ chop			
Lamb, roast3"x2½"x1¼"			
Beef, roast3"x2" x1¼"			
Beef steak, broiled2"x1" x1"			
Chicken, roast3"x3" x1½"			

Group III

(No Restriction)

<i>Vegetables</i>	<i>Fruits</i>	<i>Miscellaneous</i>
Asparagus	Apple	Sugar
Cabbage	Apricot	Maple sugar
Carrots	Blueberries	Syrup
Cauliflower	Cherries	Honey
Celery	Cranberries	Candy
Cucumbers	Grapefruit	4 Dates daily
Lettuce	Grapes	3 Sunshine arrowroot
Mushrooms	Muskmelon	cookies daily
String beans	Lemons	Cornstarch
Tomato (fresh)	Oranges	Arrowroot
Tomato (cooked)	Peaches	Tapioca
Onions	Pears	Post-Toasties
Squash	Pineapple	Butter
Turnips	Plums	Olive oil
	Prunes	
	Raspberries	
	Strawberries	
	Watermelon	

"On this sheet are most of the ordinary foodstuffs used in any home. These foods are divided into three groups according to the amount of protein in them. In Group 3, there is so little protein that one can ordinarily ignore it. In Group 1, each full portion (indicated to the right of each foodstuff) contains approximately 4 Gm. of protein. In Group 2, each full portion contains approximately 8 Gm. of protein. To make it still simpler, we avoid mentioning grams and instruct the patient that each full portion in Group 1 counts one point. In Group 2, it counts two points. The number of points for the day is inserted in the blank space left for that purpose at the top of the sheet. A low protein diet would be represented by seven points (28 Gm.). A very generous protein diet—for a nephritic patient—would be equivalent to fifteen points (60 Gm.). Another blank line for the prescription of the amount of fluid is placed immediately under the prescription of protein. The physician may use his own discretion about allowing tea or coffee or substitutes for

these. The patients are not allowed to add salt to the food after it comes to the table. The average patient under this regimen does not get more than 4 or 5 Gm. of salt a day. If he is edematous, we can still further decrease the salt by ordering fresh butter, salt-poor bread, vegetables, meats, etc., boiled free from salt, and, if necessary, the use of distilled water whenever water is used in the diet. The former method reduces the salt intake to approximately 2.4 Gm. a day, and the latter to perhaps as low as 0.5 Gm. a day."

The effort to build up the blood proteins in the nephrotic syndrome of glomerulonephritis by means of the high protein diet may not prove successful. McCann and his associates have demonstrated by balance studies that one can deposit protein in the nephritic individual with the nephrotic syndrome without affecting the level of the blood proteins. Persistence is important.

Efforts to quickly restore the oncotic pressure by the injection of acacia solution directly into the blood stream have met with some success in ridding nephrotic patients of edema. 500 cc. of 6 per cent acacia in 0.9 per cent sodium chloride solution may be given daily or every other day for three or four injections until 90-120 Gm. of acacia have been administered. It is probably unwise to continue the administration much beyond this because not enough is known about the disposition of acacia in the body. Blood transfusions have been used for the same purpose but are not so effective.

Edema is capricious; often it mysteriously disappears and then reappears. Spontaneous diuresis may occur at times when one is using a certain drug or measure, thus establishing a false therapeutic claim for some medicinal product. These matters must constantly be borne in mind in the treatment of the nephrotic syndrome.

It has long been accepted that diuretics were contraindicated in glomerulonephritis. Then, following the bold administration of proteins in genuine nephrosis, various powerful diuretics were employed and finally cautiously administered in the nephrotic stages of glomerulonephritis. The xanthine group—caffeine, theobromine and theophylline—are not of much value. Urea in large doses, 15 to 20 Gm. three times daily, is sometimes successful, but urea is expensive and is not pleasant to take. The mercurials, salyrgan and mercupurin, injected intravenously or intramuscularly have been successful in combating various kinds of edema, especially that of

cardiac origin and that occurring in genuine nephrosis. They are potent drugs, capable in true nephritis of producing severe reactions, stomatitis, hematuria and colitis. The closer the clinical picture is to genuine nephrosis the less dangerous is their administration. Mercupurin—a combination of mercury and theophylline—is widely used and seems less likely to cause reactions. It is wise to administer it the first thing in the morning; otherwise, the patient may exhaust himself at night urinating. A test dose of 0.5 cc. is first given. Acid-producing salts in large doses are often combined with salyrgan and mercupurin: ammonium chloride or nitrate, 6–10 Gm. daily, in enteric-coated capsules. One must be on guard for acidosis by occasional estimations of the carbon dioxide combining power of the blood plasma. These salts aid in the elimination of edema probably because they promote the excretion of base and with it water. Keith and Binger now prefer potassium nitrate—enteric-coated pills of 0.5 Gm. each, 4 to 6 three times daily after meals. This is less likely to cause toxic symptoms.

Sweating and purging are best not used in this form of edema. The aspiration of effusions is sometimes necessary.

The salt intake in health is about 5 Gm. daily. Taking the salt-shaker away will cut this amount in half and produce a "salt-poor" diet. Cooking without salt, substituting salt-free bread and butter, and choosing other salt-poor foods, will bring about more rigid restriction, but this is unnecessary. It makes the diet unpalatable, further interferes with the appetite, and thus adds to the already difficult problem of maintaining nutrition. Salt substitutes (make certain that they are not sodium salts), lemon, vinegar and onion, may be used to flavor the diet.

Salt restriction is important in "the nephrotic syndrome," but there is no necessity for rigid fluid control.

CHRONIC GLOMERULONEPHRITIS

As the disease becomes chronic it is increasingly important (1) to maintain nutrition, and (2) to provide sufficient fluid to accommodate the compensatory polyuria. In other words, it is the loss of concentrating ability (measured by specific gravity tests) in progressive chronic glomerulonephritis that

determines the necessity for increased fluid intake. The less the concentrating ability the more fluid is necessary in order to excrete the same amount of waste substance.

An effort should be made to keep the urinary output at 1500-2000 cc. a day. It is not the amount of fluid taken in that is important; it is the amount available to the kidney. However, one must remember that on account of the delay in excretion very large amounts of fluid may be dangerous in marked renal insufficiency, adding an intolerable burden to the heart and brain. The patient must avoid exposure, and all efforts should be made to protect him against acute infections which may cause exacerbations.

It is important for the patient with chronic glomerulonephritis not to become pregnant; if pregnancy should occur it is sufficient reason for therapeutic abortion. Such efforts may postpone uremia, but there is no specific treatment that will restore renal tissue.

PYELONEPHRITIS

This brings us to the important question of pyelonephritis. Pyelonephritic contracted kidney accounts for an important group of cases thought to be chronic glomerulonephritis. We must pay more attention in the future to acute pyelitis and pyelonephritis of childhood and pregnancy as possible forerunners of chronic kidney disease. Too often the pyelitis of childhood is regarded lightly. It is a serious disease, capable through progression and exacerbations of causing much kidney damage. The presence of pus in the urine calls for a diagnostic study, including the bacteriology of the urine, the status of renal function and the question of urinary drainage. For the latter purpose intravenous pyelograms and sometimes cystoscopic studies are necessary. It is not sufficient simply to determine the presence and variety of bacterial infection; very often an obstructive lesion is responsible for the infection.

With the availability of drugs which act differently on various organisms it is now possible to control many cases of pyuria. Sulfanilamide is a very useful drug in the case of urinary tract infection, but its effectiveness depends upon the type of organism and the concentration of the drug in the urine. In the presence of renal damage, it must be used with

special caution because of cumulative effects. Cutting down on the fluid intake will bring about the required concentration of sulfanilamide in the urine. Thus in the case of staphylococcus infections, if the fluid intake is regulated so that the output will be about 1000 cc. daily, the administration of 1 to 1.5 Gm. of the sulfanilamide daily will result in a urinary concentration of 100 to 150 mg. per cent, which should be effective in controlling the infection. For colon bacillus infections the effective concentration must be from 200 to 250 mg. per cent, and for *Bacillus proteus* infections 300 to 350 mg. per cent of sulfanilamide in the urine is most effective.

The drug seems to act best in an alkaline urine and it is therefore well to give from 10 to 15 grains of sodium bicarbonate three times a day with the sulfanilamide. The patient must be watched for toxic effects and when a rash, fever, or rapid decrease in the red blood cell or leukocyte count appears, its administration must be stopped immediately. The drug should be continued for four to six days after the urine becomes sterile, then discontinued and a further culture made after a three-day interval. Sulfanilamide is ineffective in the treatment of infection due to *Streptococcus faecalis*. Here a bactericidal agent that acts in an acid medium is necessary.

The ketogenic diet was the original form of administering an organic acid, but because of the difficulties attending its use, it was replaced by mandelic acid. Mandelic acid is bactericidal at a pH below 5.5 and at a concentration greater than 0.5 per cent. It is best to test the pH of the urine with nitrazine paper to make sure that it is below 5.5. If necessary, ammonium nitrate (0.5 Gm. four times a day) may be given in addition if the acidity is not great enough. The excretion of mandelate is almost entirely by the kidney, so that a dose of 1 Gm. per 100 cc. of urinary output practically assures a concentration of 0.5 per cent. The usual adult dose of 45 grains (3 Gm.) four times a day is given to children from twelve to fifteen years of age. Infants can take 10 grains (0.65 Gm.) four times a day and, depending on urinary output, a gradually increasing dose with age up to the adult dose.

Mandelic acid often produces a sterile urine culture within twenty-four hours, but it is better to continue treatment three or four days thereafter, and then after a further interval of

three or four days culture is repeated. A sterile culture at this time indicates recovery.

To continue the discussion of chronic kidney disease it may be said that as concentrating ability fails (specific gravity about 1.010, urea clearance less than 20 per cent), blood non-protein nitrogen mounts and serves as an index to approaching uremia. Until this occurs it is unnecessary to limit the protein for the sake of the kidney, and even then proteins should not be too restricted, probably never less than 40 Gm. a day for any extended period.

To the nephrotic edema of the second stage of glomerulonephritis may be added cardiac edema in the terminal stages. This is especially apt to occur in nephrosclerosis. It calls for cardiac remedies, especially digitalis, and salt and water restriction.

The anemia of chronic nephritis cannot be treated successfully. It is important not to add to it by the long-continued use of anemia-producing (low-protein) diets. Transfusions give temporary help only.

If a patient with chronic nephritis can afford it, a warm climate in winter, to avoid respiratory infections, is advisable. Foci of infection (teeth and tonsils) may be removed in chronic glomerulonephritis. Do not hope for too much from the standpoint of benefiting the disease. In fact, if renal function is severely impaired an operation had better not be done as it may precipitate uremia. Prerenal deviation of fluid by vomiting, diarrhea, heart failure, and infections, may precipitate uremia in chronic nephritis with renal insufficiency because not enough fluid is furnished to the kidney to carry on its important task of getting rid of waste.

NEPHROSCLEROSIS

The treatment of nephrosclerosis, that is, the renal part of the picture of hypertensive-vascular disease, does not differ from the symptomatic management of the progressive loss of kidney function in glomerulonephritis. There is no specific drug or organ extract that will stop the process. The principles of management are the same: to maintain nutrition and supply an adequate amount of fluid for the compensatory polyuria.

When it comes to the question of renal failure occurring with malignant hypertension, the treatment again is the same as in uremia arising from glomerulonephritis. This we may now briefly consider:

UREMIA

When kidney insufficiency can no longer be adequately compensated by polyuria, blood nonprotein nitrogen figures rise. Blood urea clearance values remain below 20 per cent before nitrogen retention occurs. This is known as the state of renal failure producing the clinical picture of uremia. Death, usually within a short time, is inevitable although it occasionally can be delayed for many months.

Efforts in the past have been directed solely to the lowering of the blood nonprotein nitrogen. A more rational viewpoint now recognizes that the increased nonprotein nitrogen is only an index to the uremic state and not the cause. Hence, treatment should be directed primarily not to this symptom but to the fundamental basis of the disease.

The principles of treatment are similar to those discussed for chronic glomerulonephritis, but the problem is even more difficult because of the precarious state of the patient. One must be concerned with (1) the promotion of an abundant flow of urine, (2) special efforts to maintain the nutrition, and (3) the general care. The great difficulty exists that the therapeutic weapons employed are double-edged swords. If one furnishes sufficient fluid to promote an abundant flow of urine, it is possible to impose an added strain on an already burdened heart or edematous brain; if one attempts to stimulate excretion of waste products through other channels, such as the skin and bowel, one removes fluid that the kidney could well use and at the same time takes a chance on adding further strain to a damaged cardiovascular system. Purgation may precipitate colitis, which is occasionally a terminal event anyhow.

In regulating the diet, protein may be somewhat restricted (30-40 Gm. daily), but not absolutely prohibited as is so often attempted. Nitrogen equilibrium must be maintained, and this calls not only for sufficient protein but for an adequate amount of carbohydrate to help utilize the protein. Sometimes dietary principles must be entirely forgotten for a

time in order to meet the whims of appetite and the digestive needs of a very sick patient.

Acidosis is very apt to be present. It is responsible for air hunger. Sodium bicarbonate or citrate may be used to combat it, always remembering that the disturbed acid-base equilibrium may be quickly upset in either direction. Frequent carbon dioxide combining power and plasma chloride estimations may be essential in determining the state of acid-base equilibrium and the electrolyte balance. Low plasma chlorides call for the administration of sodium chloride.

Vomiting is a distressing symptom which leads to dehydration and starvation and causes the blood nonprotein nitrogen to mount rapidly. Cocaine, $\frac{1}{4}$ grain by mouth every three hours, may be used and gastric lavage may be tried. It may even be necessary to stop all nourishment by mouth and to give fluid by other channels. Under these circumstances constant duodenal suction may be tried in an effort to eliminate products of intestinal putrefaction. Five per cent glucose intravenously has been found very useful and normal salt solution combined with it to overcome the loss of chloride from vomiting.

Hyman has employed for this purpose the continuous intravenous drip which admits fluid very slowly into the vein and permits large quantities to be given in twenty-four hours. The fluid should not be given faster than 200 cc. per hour intravenously.

Small blood transfusions are frequently administered, but it is questionable if they do more than temporary good. It is important to keep the mouth clean. Itching may be an intolerable symptom. O'Hare recommends sponging with vinegar or weak acetic acid. Calcium by mouth or intravenously is often used for muscle twitchings but it is not always successful. Pericarditis is a frequent terminal event which may be signaled by a sharp pain in the precordium. Morphine, formerly erroneously thought to be an inhibitor of renal secretion, may be given for this symptom as well as for the other distressing symptoms that have been mentioned. The only precaution is that observed for any potent drug administered to patients with defective renal function: one must look out for cumulative effects.

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THE VARIOUS FORMS OF ASTHENIA

ASTHENIA may be defined loosely as a loss of strength or power. It is defined more specifically as "a want of bodily vigor; debility; diminution of the vital forces." (Webster.)

It is of course clear that asthenia is merely a symptom which may be encountered in a wide variety of diseases, both of a neurological and non-neurological nature. Indeed, a hasty consideration of the symptom indicates that asthenia in some form is present in practically every illness, since almost any systemic disease is attended by loss of strength or bodily vigor. This, however, is much too broad a view of the problem; to include these forms of asthenia would necessitate a consideration of diseases beyond the scope of this discussion.

TYPES

Asthenia may occur in two main forms:

Transitory Asthenia.—This form has just been referred to and is found in the course of all sorts of systemic diseases. It persists only as long as the disease itself or for a short time thereafter—as, for example, the asthenia which occurs with acute infections. Similarly, asthenia may be found prominently in the course of chronic systemic disorders such as tuberculosis, diabetes, etc.

Constant Asthenia.—It is this form of asthenia which concerns us primarily. It is found as a constant or almost constant symptom in a variety of disorders, and it is characterized in these conditions, furthermore, by the fact that it is prominent and at times the outstanding symptom.

CLASSIFICATION

As already indicated, it would be impossible to indicate all the disorders in which asthenia occurs since the symptom is found widely as a transitory manifestation in all sorts of systemic disorders, both acute and chronic. A working classification of the disorders in which asthenia occurs as a more or less permanent manifestation is possible, however.

A working classification may be indicated as follows:

I. Transitory Asthenia.

(A) Acute Systemic Disorders:

1. Acute infections of all sorts, and acute nutritional, degenerative and metabolic disorders.
2. Chronic infections or degenerative states:
Diabetes, tuberculosis, nephritis, arteriosclerosis.
3. Involutional processes (senility).

II. Constant Asthenia.

(A) Muscular Disorders:

1. Myasthenia gravis.
2. Myopathies of other sorts, such as progressive muscular dystrophy.

(B) Endocrine Disorders:

1. Adrenal syndromes.
2. Pituitary syndromes.
3. Thyroid syndromes.

(C) Psychogenic Disorders:

1. Neurasthenia.
2. Psychasthenia.
3. Anxiety states.

(D) Miscellaneous:

1. Narcolepsy.

These are the most important conditions in which asthenia is found as a prominent symptom.

MYOPATHIES

Myasthenia Gravis.—Among the more important disorders in which asthenia is a prominent symptom is myasthenia gravis. This is a disorder of adolescence and adulthood which is characterized by weakness of the voluntary muscles. It is important to recognize because it lends itself quite satisfactorily to drug therapy.

The disease appears usually between the ages of twenty and thirty-five, and is more common in females than in males. No specific cause is known, but it may become manifest after

such infectious diseases as influenza, encephalitis, or typhoid fever. It is often associated with exophthalmic goiter.

The striking *symptom* of this disorder is the muscular weakness which usually develops gradually. The onset is often with weakness of the eye muscles; hence, a complaint of ptosis or diplopia is quite common. Indeed, there are cases in which most of the manifestations of the disease are in the eye muscles or in the eye muscles and the muscles of deglutition and chewing. The muscles of the arms and hands are also affected frequently, and less often, those of the legs.

The outstanding complaint on the part of the patient is weakness. This weakness is characterized by: (1) its onset after exertion, and (2) its relief by rest provided the disease has not advanced too far. The onset with use or exertion of the muscles may be noticed in many ways: thus, reading or watching a moving picture may cause ptosis of the eyelids or diplopia; talking may result in a gradual weakening of the voice, resulting in eventual aphonia; chewing may induce a complete weakness of the muscles of mastication, so that jaw movements are no longer possible for the moment; and writing may result in weakness of the hand muscles of such a degree that it is no longer possible to write. These and similar complaints are found early in the disease. If the disorder has not progressed too far, the weakness will disappear on resting for a minute or two, following which the eyelids will again open, the voice again regain its volume, and chewing once more will be possible. All these muscles, however, will become weak again on repeated use. Sometimes, general weakness or fatigue is an early manifestation of the disorder.

On *examination* one finds a striking facial appearance. There is a look of apprehension and anxiety, though these patients generally show smoothed-out facial muscles. The brow is smooth, there is usually partial ptosis, and the facial muscles have a pudgy, smooth appearance. There may be ocular palsies of varying degree, from an isolated external rectus weakness to complete bilateral ophthalmoplegia. It is these cases of ophthalmoplegic myasthenia which are confusing and are often missed. Weakness of the arms and legs may vary from slight weakness to almost complete paralysis. Atrophy of the muscles is not present and fibrillations are

never seen. The muscles often have a pudgy feeling. The reflexes are normal early in the disease but may become lost later. Sensory disturbances are not found.

Laboratory studies are usually not helpful. There may be an increased output of creatine in the urine, with a decreased creatinine output, but this is not constant. α -Ray studies may reveal a persistently enlarged thymus gland at times. Electrical examination may reveal the Jolly reaction, which is characterized by a progressive decrease in the reaction of a voluntary muscle on repeated faradic stimulation. The reactions to galvanism remain normal. The Jolly reaction is characteristic when it is found, but it is not always present early in the disease.

In a suspected case of myasthenia gravis, simple *clinical tests* will often establish the diagnosis. These consist of the following: (1) if the patient is asked to look at an object intently, a gradual drooping of the eyelids will be noted, (2) repeated chewing movements will result often in eventual cessation of the movement, and (3) repeated opening and closing of the fists will result in a gradual loss of power and eventual inability to perform the movement.

The *diagnosis* is therefore not difficult in typical cases. In cases with ophthalmoplegia, differentiation must be made from multiple sclerosis and midbrain tumor. The history of onset with exertion and recession with rest will be of great help. In multiple sclerosis there will be optic atrophy, absent abdominal reflexes, probably nystagmus, and possibly other signs, such as spastic paraplegia. In midbrain tumor there will be a progressive history, often hemiparesis, sensory disturbances, and often choked disc. Hysteria is a common mistake in diagnosis in cases which begin with aphonia. A careful history will reveal the difference in the two disorders; in hysteria, there will be a history of neurotic personality, an acute onset, and evidence of a precipitating cause of the aphonia. Chronic, progressive bulbar paralysis is sometimes diagnosed in cases in which patients have difficulty in swallowing and chewing. In such cases there is atrophy of the tongue, facial muscles and fibrillary twitchings.

Of the greatest value in diagnosis is the *prostigmin test*. This consists in the subcutaneous or intramuscular injection

of prostigmin in doses of 1 cc. (1.5 mg.). If no response is obtained with this dosage, 2-3 cc. may be given. In such cases one observes, in the course of about thirty minutes, a gradual disappearance of the ptosis and ocular palsies and a subjective sense of well-being in the patient resulting in increased muscular strength in all the muscles. The result in many cases is dramatic, but in some there is never complete disappearance of the weakness.

The *treatment* of myasthenia gravis has therefore been greatly advanced by the use of prostigmin, a synthetic physostigmine compound. This may be given by injection at first, in amounts as high as 3-6 cc. a day. For continued use the drug may be given by mouth in 15 mg. tablets. The number of tablets necessary to maintain improvement varies with the individual case and must be worked out for each case. The dosage may be as high as one 15 mg. tablet every hour, or as low as one tablet four times a day, depending on the severity of the disorder. Atropine, in doses of gr. 1/200, should be given once to three times a day to prevent intestinal disorders.

Most patients with myasthenia improve greatly with prostigmin, but some respond only slightly. In such cases the addition of *ephedrine sulfate* (gr. $\frac{3}{8}$, three times a day by mouth) often helps a great deal and improves muscle power better than with prostigmin alone. *Potassium chloride* (10-20 Gm.) in water by mouth is sometimes of value. Glycine is of no value. Light massage is often helpful given once a day. Vigorous massage is of no value since it induces muscular fatigue.

A typical example of the *ocular type of myasthenia gravis* is given in the following case:

Myasthenia Gravis in a Patient with Ptosis, Diplopia, Dysphagia, and Weakness of Mastication. Good Response to Prostigmin Diagnostically and Therapeutically. No Involvement of the Limbs:

History.—This patient, a man of thirty-nine, was referred by Dr. Paul M. Corman of Bellefonte, Pa. He was seen in August, 1937, and stated that he had had diplopia for three months, ptosis for two months, and dysarthria for three weeks. He had been well until May, 1937. At this time he noticed trouble with his eyes and he saw double. The diplopia persisted and was followed by a drooping of the eyelids one month later, the right lid being involved first and then the left. His condition persisted in this fashion until three weeks before he was seen, when he developed difficulty in swallowing, with regurgitation of liquids through the nose. His jaws then became fatigued on chewing. He had no fatigue in his limbs.

Examination revealed ptosis of both eyelids, bilateral external rectus weakness, weakness of the masseters and pterygoids, and weakness of all the facial muscles. There were no other pertinent findings. Physical examination revealed an enlargement of the thyroid gland, but the basal metabolic rate was $-4\frac{1}{2}$. All other laboratory tests were negative.

The patient was given 2 cc. of prostigmin and showed a marked improvement in his ptosis, ocular and masseter weakness. He was then placed on prostigmin by mouth, taking 2 tablets (30 mg.) every hour and 3 tablets (45 mg.) every third dose. He was able to tolerate this dosage well and was much improved except for persistence of his diplopia.

In the following we see a case of full-blown myasthenia gravis:

N. F. (Jefferson Hospital No. BH3952). Onset with Diplopia. Weakness of Hands and Arms, Followed by Weakness in Swallowing and Drooping of Eyelids. Objective Weakness of Ocular Muscles, Face, Palate, Arms. Reflex Changes. Good Response to Prostigmin and Ephedrine.

History.—The patient, a man of fifty-four years, entered the Jefferson Hospital on October 9, 1938, under the care of Dr. S. J. Thornton. He complained of muscular fatigue. He had been well until January, 1938, ten months before entrance, when he had noticed that he saw double while at the moving pictures. He found that his diplopia was not present in the morning after a night's rest, but that it tended to appear in the evening. Within a week after the onset of this diplopia he developed weakness of his hands and noticed difficulty in writing. This too was more pronounced toward the close of day. He had found that a few hours rest in bed revived his muscular power. Following the weakness in his hands, he developed in rapid succession weakness of the legs, difficulty in swallowing, and drooping of the eyelids. About two weeks before entrance into the hospital he awoke one morning to find that he was unable to swallow, talk, or cough.

Examination revealed a moderate degree of ptosis bilaterally, a slight weakness of the left external rectus muscle, weakness of all the muscles of the face, complete immobility of the palate, severe weakness of the muscles of the shoulder girdles and arms, but good power in the legs. There was no atrophy of the muscles. The biceps reflexes were decreased, the triceps absent bilaterally; the patellar reflexes were active and the achilles decreased. Sensation was normal everywhere.

Treatment consisted in the administration of prostigmin, to which the patient reacted very well. He was revived by the prostigmin when he found he could not talk, swallow, or cough a few weeks before entrance into the hospital. At this time he showed definite evidence of pulmonary edema. He is now on a combined treatment of prostigmin and ephedrine by mouth and is doing very well.

This case illustrates the typical onset of myasthenia with muscular fatigue involving, first the eye muscles, then the muscles of the arms, and finally the bulbar muscles. As a rule the last are involved before the limb muscles, but the weakness

may develop according to the pattern observed in this instance. The history of improvement in the morning after a night's rest and aggravation of symptoms during the day after muscular exertion is characteristic and practically makes the diagnosis. The response to prostigmin was typical. The electrical reaction was found to be characteristic. The laboratory tests were not significant; the basal metabolic rate, glucose tolerance test, creatine excretion, and x-ray of the thymus gland were all negative.

These well-marked cases are therefore not difficult to diagnose. It is the early cases which require care. In cases with only diplopia and ptosis and no other signs of myasthenia gravis, the effect of prostigmin should always be tried out even if no other muscles are affected. The same holds true of other obscure cases of muscle weakness or fatigue. The drug causes no discomfort if protected by atropine, and a therapeutic test may disclose an unsuspected case if prostigmin is used as a diagnostic procedure.

Other Muscular Dystrophies.—Weakness or asthenia is a common symptom of many of the myopathies. These are disorders which involve the muscles primarily, without disease of the peripheral or central nervous system. They include such diverse disorders as myotonia congenita, progressive muscular dystrophy, myotonia congenita and atrophica, scapulo-humeral dystrophy, facio-scapulo-humeral dystrophy, and other disorders. Their clinical manifestations vary greatly, but they have in common the symptom of muscular weakness or asthenia.

The mechanism of the weakness varies, of course, with the type of disorder. Thus in myotonia congenita (Oppenheim's disease) the weakness is found with a flabby musculature from early life. In pseudo-hypertrophic dystrophy, the weakness is accompanied by degenerative changes in the muscles. In myotonia congenita, it is associated with increased irritability of the muscles. In other forms, such as in myotonia atrophica, facio-scapulo-humeral and scapulo-humeral dystrophy, muscular atrophy forms the basis of the weakness. Unfortunately the mechanism of the weakness, just as the reason for the myopathy, is wrapped in obscurity in every one of the myopathies.

The *treatment* of the asthenia in the myopathies is extremely unsatisfactory. Glycine is used because of the disturbance in the metabolism of creatine in almost all the types, but it is unsatisfactory and seldom yields good responses. Ephedrine is likewise unsatisfactory. Quinine (gr. 5) three times a day is valuable in many but not all the cases of myotonia congenita (Thomsen's disease) and myotonia atrophica.

ENDOCRINE DISORDERS

Adrenal Syndromes.—Asthenia is known to be a prominent and important symptom of disease of the adrenal glands, particularly Addison's disease. Asthenia and undue fatigue is invariably present in Addison's disease and is usually the first symptom. It consists of an unexplained, undue fatigability noticed in a tendency to tire more easily than usual. The asthenia is usually worse in the morning, as well as following infections and over-exertion. There may be periods of remission during which the excessive muscular weakness disappears. The asthenia due to adrenal insufficiency, as seen in Addison's disease, is accompanied by skin pigmentation, a low blood pressure, and low blood sugar and chlorides. Gastro-intestinal symptoms, such as anorexia, constipation, loss of weight and inanition, complete the picture. Remissions and crises occur during the disease, the latter being marked by an increase in the gastro-intestinal symptoms, fall in blood pressure, hypothermia, and often by mental symptoms.

The asthenia in Addison's disease is probably the result of disturbed muscle metabolism, since one finds in this disorder a prolonged increase in blood lactic acid following exercise, a low blood sugar, a flat sugar tolerance curve, and possibly delayed absorption of sugar from the gastro-intestinal tract.

The *treatment* of asthenia in adrenal insufficiency consists of: (1) sodium chloride in large amounts by mouth (10-30 Gm. a day), (2) cortical hormone given by subcutaneous injection (1-5 cc. daily), and (3) a diet low in potassium.

Pituitary Syndromes.—Asthenia is a common symptom in most of the pituitary syndromes. It is found in hypopituitary states, whether due to tumor or to glandular insufficiency; it is found also in acromegaly, and in pituitary cachexia or Simmonds' disease.

In the *hypopituitary* syndromes (adiposogenital dystrophy) the asthenia is incidental to a group of other more prominent complaints, but it is none the less disturbing to the patient. A gain in weight, menstrual disturbances, impotence, headache, and visual disturbances are very prominent. The asthenia is dependent probably on a disturbance in carbohydrate metabolism and on a deficiency of the anterior pituitary hormones.

The asthenia of *acromegaly* is likewise incidental and not a prominent feature of the disease. Despite the enlarged stature and the relatively prominent musculature of the acromegalic, there is a subjective decrease of muscle strength as well as an objective loss of power. There may be early in the disease a sense of increased strength, but eventually the acromegalic suffers from a progressive weakness amounting to a true asthenia. This fatigability and decreased strength are in striking contrast to the enlarged skeletal framework and the well-preserved muscles. The recognition of asthenia in acromegaly should offer no difficulties in view of the typical skeletal deformities which accompany the disease. Usually, but not always, there is an accompanying pituitary tumor associated with loss of vision, bitemporal hemianopsia, and deformity of the sella turcica. The other features of acromegaly are too well known to require repetition.

Asthenia in pituitary conditions is best illustrated by Simmonds' disease, or *pituitary cachexia*. This disease may occur at any age. It is rare and is characterized by a progressively developing clinical picture with great loss of weight (resulting in severe emaciation), by an atrophic skin, anorexia, great weakness, loss of hair, loss of sexual potency or menstrual suppression, and mental deterioration. Gastro-intestinal symptoms are common; achlorhydria or achylia gastrica may be present. Secondary anemia is usually present, and the basal metabolic rate is low. The etiology varies greatly; there is destruction of the anterior lobe of the pituitary gland by involutional processes, adenoma, or metastatic carcinoma.

The weakness which is found in pituitary cachexia is an outstanding feature of the disease. It is often the most prominent complaint. Excessive fatigability is prominent. Exertion of a mild degree often results in great fatigue and sometimes in collapse. Indeed, the asthenia in cases of pit-

uitary cachexia may be as pronounced as in cases of Addison's disease.

Early in the disease there may be little to note except progressive weakness and loss of weight, with no objective findings to support the complaints. As a result, patients with this disease are frequently diagnosed as neurotic, the real nature of the disorder not becoming apparent until later in the disease. Early in the disorder the diagnosis may be extremely difficult. Later, the gastro-intestinal symptoms, the anemia and achlorhydria, the marked involvement of the ectodermal tissues (dry, atrophic skin, loss of teeth and hair) and sexual impotence or menstrual difficulties make the diagnosis easier. The sella turcica shows no constant findings; it may be enlarged if the disease is secondary to a tumor, but it is often normal.

Treatment is unsatisfactory. The disease progresses despite daily injections of anterior pituitary hormone, thyroid medication, and rest. Pituitary extract by mouth is of no help. Injections of the extract (1-2 cc. daily) may be of help for a time, but eventually they lose their effect. Because of the low metabolic rate which is often found in the disease, thyroid extract is given, usually without avail.

Thyroid Disorders.—Muscular weakness is a common complaint in hypothyroid states, but it is usually a minor factor in the disorder. True asthenia is more prominent in hyperthyroidism. It may reach quite a profound degree in advanced cases, with severe muscle wasting. These cases may simulate closely those of generalized muscular atrophy. The mechanism of the weakness in such cases is not clear, but it may be related to the depletion of glycogen stores and the increased use of the sugar in the muscles.

PSYCHOGENIC DISORDERS

Among the most common causes of asthenia are various types of *neuroses*, such as neurasthenia, psychasthenia, and anxiety states of other sorts. The complaint of excessive fatigability or weakness which is found in these and other neuroses has no specific implication. It must be regarded as a symptom for which a meaning must, if possible, be found.

Despite this lack of specificity, there are certain features

of the great fatigability of neurotics which require emphasis. It is present on waking and usually persists throughout the day. Often it is worse toward the end of the day, but sometimes it tends to wear off as the day goes on. Neurotic patients often complain of waking up fully as fatigued as when they went to bed, which is not an uncommon complaint in normal people but is doubly significant in neurotics. The fatigue in the neurotic, moreover, has little relation to physical labor. It is characterized by great fatigability in situations of great emotional stress, and is readily relieved by removal from such situations.

It is typical of neurotic fatigability that there may be a striking metamorphosis from great fatigue and weakness to complete restoration of vigor as the scenes shift from those of emotional stress to removal from all emotional tension. This story may be offered spontaneously by the neurotic or it may be elicited readily in the history. There is the further feature in that the fatigue which is seen in neurotic cases is out of all proportion to either the physical or mental stress to which the patient is subjected, the least physical or mental exertion eliciting a marked response. This disproportion between apparent cause and effect is an important diagnostic feature of neurotic fatigue.

Great fatigability is most pronounced in *neurasthenia*, in which one finds both physical and mental fatigue, numerous complaints referable to all parts of the body, sensations of pressure in the head, paresthesias, anorexia, palpitation of the heart, inability to concentrate, and a host of other symptoms. Among these fatigability is very prominent.

Cases similar to neurasthenia were observed during the war under periods of great stress and were described as ones of *neurocirculatory asthenia*. Similar episodes of fatigue are found in anxiety neuroses, which are characterized by great anxiety and a variety of somatic complaints.

The *diagnosis* of asthenia due to neurotic conditions is not difficult. Emphasis must once more be placed on the fact that the asthenia is only one of many symptoms, but is none the less a very prominent one. The history is helpful in its extreme indefiniteness. A study of the personality reveals fertile ground for a neurosis by the presence of an unstable person-

ality. Physical examination is negative and reveals no basis for the numerous somatic complaints. Most important of all, however, one usually finds that there are evidences of emotional maladjustment which can readily account for the complaints. These are as a rule sufficient to establish the diagnosis of neurosis. The only logical *treatment* of the asthenia seen in neurosis is to treat the neurosis itself.

Fatigue is a common feature also of the neuroses which follow trauma. In these neuroses there is inability to apply oneself either physically or mentally without great fatigability.

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DRUG ADDICTION

FROM time immemorial the human mind has ever sought ways and means not only to escape the drab monotony and routine which it constantly encounters, but also methods of escaping those unpleasant complexities which arise in the course of human relations. The methods of such escape vary with different periods of history, the different strata of society and with the individual characteristics basically found in different personalities. Where one man may take a trip, go to a ball game, or take a nap after dinner, another ingests some substance which more than just removes him from the scene of his activities and carries him into the realm of unreality. Still others may escape by having an hysterical amnesic episode, a period of day dreaming, or even severe mental disease.

The substances employed vary from a glass of water through which some illuminating gas has been passed, up the line through the barbiturates and narcotics such as morphine, heroin, and the marihuana group, all the way to alcohol, which is probably the most common. To any of these an individual may become addicted, and when he has become so addicted, he is a problem for the medical man even though it must be admitted that many such patients are probably medical and psychiatric problems long before they become inebriates.

It is sometimes difficult to know just what one means by the term "addict." However, it is generally agreed that an individual who consumes any drug constantly, who is unable to stop using that drug, and who when taken off the drug by some means or other suffers physical or mental discomfort or even collapse, can be called an addict. This may be distin-

guished from the habitual user of a drug: the individual who is accustomed to using a drug but is not necessarily dependent on it and who can, if he so desires, stop using it without suffering any physical or mental symptoms.

The drugs used over the world vary from place to place, and in different parts of the world certain drugs are used more than others. For example, in Canada, codeine is especially used; in the United States, marihuana and hashish are often used in cigarettes. In Mexico, a drug named "mescaline" is frequently used. So it may be that from place to place throughout the world a different drug takes preference; however, the basic condition and effects are probably about the same.

The method of administration of the drug may be by inhalation, by ingestion, or by hypodermic. Some are addicted to ether, chloroform, or nitrous oxide and inhale large doses of these and obtain a "drunk" that way. One dentist whom we knew used to inhale nitrous oxide frequently and later became an alcohol addict. Atropine has also been used for this purpose.

The cause of drug addiction is a much discussed subject, and undoubtedly there are many different causes, both predisposing and exciting. In a study made by Kolb and Ossensfort, those addicted to drugs were divided into certain groups: (1) The normal individual who becomes accidentally addicted, either because he has had some serious illness where the drug has been given to him or because of pain, and who is unable to stop the use of the drug of his own accord; (2) the psychopathic individual, who gets into difficulty frequently and because of his inability to cope with life's complexities takes a drug as a way out; he in turn becomes addicted and is unable to stop without help; (3) the psychoneurotic individual, who takes drugs because of his various symptoms which, however, are on a psychoneurotic basis; (4) the person who is already an inebriate of some sort and then takes another drug or two because of that. (One patient we saw at the Philadelphia General Hospital last year was taking morphine, alcohol, phenobarbital and bromide, all at the same time. However, he did not start with all the drugs at once, but one had led to the other in an attempt to keep up the original effect.); (5) a frankly

psychotic person, who takes drugs because of his mental illness; and (6) finally, the individual who is psychotic from drugs; although this is rare with the user of opiates, it is most common with the alcohol addict.

It may be said that by and large the commonest single cause of drug addiction is a psychopathic personality, although the individual has in turn been introduced to the drug probably by a physician, an addict, or by a companion.

Much was written at one time about the allergic nature of drug addiction, and it was on this basis that some of the treatments of withdrawal were developed in order to remove the sensitivity involved. Some of these studies, such as those made by Natle, do indicate, however, in a more scientific way what most individuals in this field already know, namely, that the amount of a drug necessary to produce a given effect in an individual varies greatly. In his study with alcohol, Natle found that in a person who was sensitive to the drug about $\frac{1}{4}$ ounce of alcohol was sufficient to cause demonstrable signs, whereas in people not sensitive to the drug, about $2\frac{1}{4}$ ounces were necessary to produce signs of intoxication. It simply points out again that some people are born neuropsychiatric millionaires and others are born neuropsychiatric paupers. It may be demonstrated in the way a person reacts to a situation in life and also in the way he reacts to drugs.

One of the causes frequently ascribed to a person's becoming addicted is insomnia. Thus an individual who for some reason or other is not able to sleep and who begins to take barbiturates, paraldehyde, bromides, or some similar substance and finds it increasingly necessary to take the drug to sleep, may after a time become addicted to one of them. The question is often raised in such a situation whether the sleeplessness is the underlying cause or whether the condition which causes the person to have insomnia in turn allowed him to become easily addicted to the use of some drug.

The incidence of drug addiction in this country probably lies somewhere between 90,000 and 150,000. It is difficult to get accurate figures inasmuch as there are a certain large number of people who use drugs only for a period of time and who are not really addicts. The age group which is most vulnerable is from twenty-five to forty-five years.

As to the incidence of addiction in different groups, it should be mentioned that the use of drugs is more common in urban areas and among those who handle drugs, such as doctors, nurses, and pharmacists, and also in criminal groups. Cocaine, especially, is supposedly the drug of the underworld, although it is not uncommonly used by physicians.

In a study of women drug addicts who were committed to a reformatory, Hall made some interesting observations. Thirty-seven women were studied; two of them started taking drugs on their own initiative, twenty-two started on the advice of friends, and thirteen started on doctors' prescriptions. Some of these thirty-seven women had made as many as ten previous attempts at cure. They used various drugs and various methods. Hall found that this group on the whole was superior educationally and vocationally to the ordinary reformatory population, but that most came from homes with a poor social and psychologic background even though, economically, the homes were average. In the same group the addicts were unstable, maladjusted sexually and maritally, and twenty of the thirty-seven had been arrested for other offenses, namely, prostitution, larceny, or burglary. They all showed abnormal personality deviation and were all considered inadequate from a psychiatric standpoint except one. The mean I.Q., however was 96.2.

Thus it will be seen that the greatest problem in the study of drug addiction is the study of the individual personality involved, more than it is the actual immediate withdrawal of the drug.

The symptoms from the use of drugs vary from person to person, and generally it may be said that most people have a certain physical as well as mental satisfaction while taking them. However, this varies greatly, and although some people are apparently depressed from the use of drugs, they nevertheless are, temporarily at least, relieved from the immediate problems concerning them in life and so escape reality for a time.

Indian hemp with marihuana has recently gained popularity, in this country especially, because it more or less universally produces exhilaration and a feeling of well-being. It is almost impossible to give a list of the symptoms produced

in an individual except to say it is simply for him a way out, and consequently he comes back for more and more often. Some report hallucinations, loss of sense of time, dual personality. Users of mescaline may have depersonalization and find themselves in new psychic realms while under its influence.

It is generally agreed that those who use any drug over a long period of time in excessive doses develop certain personality changes. Here again the question may arise: Which is first, the personality change or the use of the drug? It is often difficult to say, and if the patient has used the drug for a long time, his natural personality may be masked by the drug and changes may therefore go unrecognized by those about him.

Detrick and Thienes, in studying experimental drug addiction with opium derivatives, found no evidence of damage to the vital organs from prolonged use of these drugs. However, it is generally admitted that alcohol, at least when used over long periods of time, may cause very definite organic change in various structures of the body, including the nervous system. While these changes may be due in large measure to secondary avitaminosis and lack of proper food during the ingestion of alcohol, they are nevertheless complications of severe alcoholism.

Alcoholic psychoses are common and, of course, may include delirium tremens, alcoholic hallucinosis, alcoholic paranoid states, and alcoholic deterioration. One also frequently sees Korsakoff's syndrome, consisting of disorientation, fabrication and other mental symptoms associated with a multiple neuritis. These patients are often sick for a period of a year or more, but recently, several patients of this sort who have come under our care have improved remarkably in two or three months with concentrated vitamin therapy, especially vitamin B.

The question of whether alcohol masks another psychosis is often brought up; *i.e.*, whether a patient is insane due to the alcohol which he has taken or whether he drinks because of or in spite of his insanity. One patient of this sort was drinking for a period of ten years and, following the withdrawal of alcohol, became acutely psychotic and has remained so for a period of two years, presenting a picture which would readily be diagnosed as hebephrenic dementia praecox. The question

here is whether the alcohol caused this mental picture, or whether the boy was a schizophrenic for some years but no one realized that he was mentally ill because of his severe alcoholism.

Another interesting case which is worth mentioning in this connection is that of a patient who, for a period of some years, drank as much as 6 ounces of paraldehyde daily, which drug was prescribed for him originally because of alcoholism. He was away on a trip for a period of several months and those who were with him said he had had no alcohol but that he had drunk up to 6 ounces of paraldehyde a day. He finally went to a doctor for treatment of the habit and, while the drug was being withdrawn, he developed a severe case of delirium tremens for a period of the next few weeks and nearly died. He had generalized tremors, his pulse was up to 160, and his temperature rose as high as 103 and 104° F., but he had no evidence of infection anywhere in his body. He finally recovered completely and has not used the drug since that time.

Cases of bromide poisoning resulting in psychosis are frequently seen. A case of this sort recently came to our attention in which the patient had as high as 550 mg. of bromide in his serum. He was acutely psychotic and looked very much like a paretic. After two weeks of treatment he was completely well. A case of barbital poisoning, where the patient had been diagnosed a paretic elsewhere despite negative findings in the blood and spinal fluid and who was given a poor prognosis (before the days of fever therapy), was completely well in six months and then gave the history that he had been taking large doses of barbital for some time before that, although the presence of hematoporphyrin in the urine led us to the assumption that he had been taking some medication to excess.

It goes without saying that the ideal treatment for any condition of this type is prevention of the use of the drug; by abolishing such drugs, there would be abolished the problem of drug addiction. However, this has already been tried in regard to alcohol and has failed. It will be tried more and more as regards the opiates, but until such a time as we have a new drug to take the place of opiates, which will give the same medical effect without the production of tolerance, habituation, or addiction, we will probably not be successful in

preventing the use of these drugs by addicts. Also, until we have a better knowledge of the physiology of addiction and until we have something better to offer psychologically inferior patients, we will have difficulty in controlling the situation.

TREATMENT

The immediate need in any case of drug addiction coming under the care of a physician is to withdraw the use of the drug. A great deal has been written on this subject and many different sorts of treatments have been devised, among which may be mentioned the use of the belladonna group of drugs, the use of peptization and water balance technic, sodium rhodanate, sodium thiocyanate, the use of rossium, the use of lipoids, and even the use of insulin and protracted narcosis. However, it is thought today that the need is simply to remove the drug in a way most comfortable for the patient; most of the other methods are oftentimes merely adding insult to injury. In an individual who has a weak habit and who is in good shape physically, abrupt withdrawal is often satisfactory. It has been estimated that about 80 per cent of addicts have a weak drug habit.

Death may complicate the abrupt withdrawal of any drug. Piker and Gelperin cited three cases and pointed out the fact that cases must be carefully selected when abrupt withdrawal is the routine procedure. If this is not done, one will experience a certain number of unpleasant results from a condition and treatment which ordinarily should not be fatal. On the other hand, in almost any individual a very slow withdrawal over a period of a month or two can be carried out safely, although this is impractical because of the period of time involved and the economic implication. In most cases, therefore, withdrawal in a period of from seven to fourteen days is carried out.

It is a generally recognized fact that there is a physical as well as a mental factor in withdrawal, as shown by the fact that if a woman who has been an addict has a child, the child has to be given a drug for the first few hours of life and then have it withdrawn in order to sustain life.

In withdrawing morphine, for example, from a patient in a rapid way, it is thought safe to assure the patient up to 3

grains of the drug in small doses between the twenty-fourth and ninety-sixth hour if necessary, and then gradually diminish it from that time on.

It must be remembered that supportive measures are frequently necessary in withdrawing any drug, whether it be morphine, alcohol, or even a barbiturate. For example, if morphine is being withdrawn, such drugs as paraldehyde, barbitol, or amytal may be used to ease the patient's distress. Ofttimes if there is any physical discomfort, the patient may have to have massage, continuous tubs and intravenous therapy to maintain body chlorides and fluids, and it may be necessary to give sugar to prevent acidosis. If alcohol is the drug which is being withdrawn, the patient may go into a state of delirium tremens, and this is probably the most severe form of withdrawal symptoms. The same measures have to be used more intensively in such a case. However, a seven- to fourteen-day period is usually sufficient to take care of the physical side of the picture and the patient can then be treated from a psychotherapeutic standpoint, which will be discussed later on.

The main thing during the withdrawal period is to make sure that the patient is properly controlled so that he can get no drug of his own initiative. It therefore becomes apparent that the best place to treat a patient is in an institution where he can be properly supervised and controlled. Such an institution is the United States Narcotic Farm at Lexington, Kentucky. Many of our states also have Inebriate Acts which cover the use of alcohol and drugs and allow such patients to be committed to mental hospitals for treatment.

Once the patient has been removed from the drug, he is no longer an acute medical problem but then becomes a psychological study. In the past there has been a great deal of emphasis on withdrawal of the drug with very little emphasis on the future of such a patient. It is a well known fact, and a most discouraging one among physicians, that most alcoholics and most drug addicts seem to relapse into their old habits after what seems to be an adequate "cure." This, of course, is not due to the fact that the patient has physical symptoms after that period, but to the fact that he is again faced with the same problems in life in which the drug previously was able to help him.

As was said before, many of these patients are psychopathic inferiors, which tends to make the problem harder; but each patient should have a thorough psychiatric and psychological study in an attempt to evaluate his ability to cope with life's situations and a further attempt should be made to guide him into some field of endeavor where life will not be so complex.

It will be noted that the addict often comes to the doctor and wants a magic cure; he wants something to be done for him in the way of specific treatment and specific medicine so that he will not have to do anything except receive the treatment given. Unfortunately there is no such cure and, because of this, many an addict has in his own mind a hopeless attitude toward recovery, or rather, we might say, he rationalizes in this way and excuses himself for not really wanting to get well.

Much has been written and said concerning the psychotherapy of drug addicts. This field has been touched on by physicians and ministers, by laymen who themselves have recovered or think they have some particular asset along this line, as well as by many kinds of quacks and charlatans. It may be said again that there is no magic cure and for that reason, probably, we have all these various individuals and types of treatments attempting to get people away from this demoralizing habit.

It would seem that the desirable thing is to have the patient assume a sense of responsibility and find some worthwhile work in life in an attempt to carry on. Something has also been written about the religious aspect of this subject. If a certain person, for example, has had experience with drugs and is converted and has determined that he should not touch the drug, and has really made up his mind to get well, he will have a better chance for a permanent result. Evangelists like Moody and Sunday undoubtedly gave many alcoholics the spark which cured them of the habit. The real answer seems to be that if a man can develop in himself or help to develop the attitude where he really desires to get rid of the drug habit and wants to face life as a normal individual, there is a great opportunity ahead.

There are certain helpful measures in enabling a person to develop the right mental attitude toward alcohol and the drug

habit, and we should not lose sight of the value of work, play and exercise. Many of these patients learn for the first time how to work with their hands, how to exercise and enjoy it, and how to have a worthwhile hobby, if they are properly guided during a period of sanitarium care. Many feel that an extra feeding given in the morning is of value—at the time when the blood sugar is a little low—as well as a cup of tea and some toast late in the afternoon at what would otherwise be the “juniper hour.”

It is well known that severe shock, either physical or mental, may at times so react upon a person that he will lose his habit. The death of a loved one, the loss of money, the commitment to a mental hospital by his family whom he did not think would do such a thing, are examples of the sort of thing which may turn him completely in regard to his attitude toward drugs. Women are probably more easily affected than men by shock.

If a patient has been given opportunity after opportunity to improve his condition and stop his habit and has not done so, then it is our feeling that he should be committed, under the laws of the state in which he lives, to a mental hospital and given the full period allowable under the law. On the other hand, it must be recognized that there are certain disadvantages to this sort of treatment; that even if a person is so committed, he may wait until his time is up with the idea in mind that “when this prison sentence is over, I will go out and drink as soon as I can and to hell with everybody.” We should also consider the family’s attitude toward having liquor in the home when one of its members has had an apparent cure from alcohol addiction. It will make life a little easier for the patient to keep temptation out of his way as much as possible, although he will be exposed to liquor in most of the places to which he goes.

SUMMARY

In summary we may then say that there are a large number of people in all countries of the world who use some drug or drugs to the point where they are unable to stop using them of their own accord and, if they do stop using them, they in turn have physical and mental discomfort.

These people are usually psychopathic inferiors. They should be hospitalized for immediate withdrawal and also for psychotherapy, and an attempt should be made to re-direct their activities and their mental trends. They should be carefully followed for a number of years after their discharge from the hospital.

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